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WORLD PCBs MAP: STORAGE AND EFFECTS IN MAN AND HIS BIOLOGIC ENVIRONMENT IN THE 1970s

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Early in the 1960s L. Goldwater planned and conducted a study on "normal" values for toxic substances in humans.[1] Under the aegis of the World Health Organization and Columbia University, this study investigated populations of 15 areas of the world and provided the first map of mercury, lead, and arsenic levels in human blood and urine. In 1965 when this study's panel of investigators was convened in Geneva, I suggested that a world-wide assessment of DDT storage in humans be done. I felt motivated to do this because intensive studies had already been conceived and undertaken by Wayland J. Hayes, Jr., under the auspices of the Communicable Disease Center of Atlanta, and by other investigators of North America and Europe, to explore this new and interesting topic. Because of the kind and valuable support of the Communicable Disease Center, Atlanta, and of Professor Hayes, the Department of Occupational Health of the Hebrew University of Jerusalem was enabled to explore the storage of DDT in humans of Israel. Later, with the kind support of the World Health Organization and particularly of J. W. Wright, Head, Vector Biology and Control, and the International Agency for Research on Cancer, Lyon, we studied the same topic in populations of Australia, Sri Lanka, Thailand, Nigeria, Kenya, Uganda, South Africa, Argentina, Brazil, and Spain. In this context we stated in 1966, that "DDT is a current constituent of the human body."[2] Eight years later we presented, in collaboration with L. Tomatis of the International Agency for Research on Cancer, Lyon, a world map of the storage of organochlorine insecticides in humans and described the natural history of this phenomenon.[3]

During the same period as we were reporting that DDT was a current constituent of the human body, S. Jensen of Karolinska University in Stockholm was opening a new pathway into the field of environmental toxicology by means of identifying the family of PCBs as pollutants of the environment and constituents of animals.[4] This discovery stimulated further studies aimed at assessing the level of PCBs in the environment and living beings, and the biologic effects of these already ubiquitous pollutants.

This report uses the scientific data available to us in an attempt to describe the epidemiologic features of the PCBs stored in man and his biologic environment and some of the effects of PCBs.

PCBs first found their use in industry in 1929. Since then they have been progressively manufactured and marketed. Except for sporadic reports in the 1930s and 1940s of the toxic effects exerted by these compounds on people occupationally exposed, they were not generally regarded as chemicals of high toxicity or as potential environmental contaminants. The large-scale contamination by PCBs of cooking oil in Japan (1968), as well as other toxic episodes, such as occurred in 1968 when 400,000 chickens died in Japan 'because of contaminated chicken feed' and in North Carolina where 75,000 eggs were destroyed (the fish-meal chicken-feed was shown to contain 400 ppm PCBs),[5] led to the restriction in the use of these compounds. They are now

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used mainly for closed electrical apparatuses, and consequently, beginning with 1971, their production has decreased.

At some time or other in the last 50 years, PCBs have become current constituents of the human body and the biologic environment. This condition is illustrated by the following data.

PCB Residues in Marine Organisms (Table 1)

PCBs were found in nearly all plants and animals from the Atlantic Ocean.[7] The lowest PCB residue levels in plankton, 0.03 ppm, were reported in the neighborhood of Scotland[8] and a relatively high level, 1.5 ppm, in the Atlantic.[7]

Atlantic hagfish collected in the Gullmar fjord had 5.0 ppm PCB liver residue levels, whereas the open-sea hagfish had only 0.2 ppm liver PCB residues.[9] Mussels from polluted areas had higher PCB residue levels, 0.017–1.70 ppm, as compared to those of unpolluted areas, 0.01–0.67 ppm.[10] Pink shrimp from the Oregon coast had very low PCB residue levels, 0.008 ppm,[11] as compared to shrimp from Escambia Bay (Fl.), accidentally polluted with PCBs, who contained up to 7.0 ppm.[12] Mussels from the Mediterranean coast of Spain had higher PCB residue levels than those of the Atlantic coast.[13]

In larger marine animals (seals, whales, sharks) PCB residue levels varied from several ppb to tens and hundreds of ppm. Grey seals from the Gulf of St. Lawrence (Canada) had a mean blubber PCB level of 14.5 ppm.[14] Seals from English waters had 212 ppm PCBs in the blubber.[15] Whales and dolphins from Canada had 0.7–147.0 ppm PCB blubber residues,[16] whereas in the Lesser Antilles these animals had only 2.7–5.0 ppm blubber PCB residues.[17]

PCB residues in male marine mammals increased with age. Female seals showed no increase of PCB residues with age.[14] Parturition and lactation may be the cause of this difference between male and female,[18] since during pregnancy the PCBs body burden is lowered by placental transfer and during lactation it is lowered through excretion in milk.

The present residue levels in marine organisms are high enough to produce toxic effects *quo ad vitam* and *quo ad futurum* and justify the efforts to reduce the contamination of oceans and seas by PCBs.[18]

PCB Residues in Fish (Table 2)

Fish constitute an important link in the food chain.

Fresh-water fish, especially fish caught in industrial countries, in rivers and their estuaries where industrial waste is disposed of, have higher PCB residue levels than those caught in nonindustrialized areas. Fish from the rivers of the eastern USA had up to 140 ppm PCBs in their flesh.[20]

Lake fish showed intermediary values for PCB residues, between those of fresh-water fish and deep-sea fish: Lake Erie fish contained up to 4.40 ppm,[21] Lake Ontario fish, 5.15 ppm,[22] Lake Michigan, 2.7–15.0 ppm,[23] Lake Superior, 1.0–5.0 ppm,[20] and Lake Superior trout 7.0 ppm.[24]

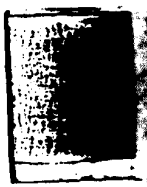
Sardines from the Mediterranean coast of Spain had 0.68–4.72 ppm PCBs, while those from the Atlantic coast had only 0.34–0.40 ppm.[13] Sardines, from the Adriatic Sea, had 0.37–1.06 ppm PCBs,[25] while sardines from the Bay of Marseilles had 0.7–5.1 ppm PCBs[26] and those from Tokyo Bay 1.0–11.0 ppm.[27]

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TABLE 1

PCB RESIDUES IN MARINE ORGANISMS

Ref.	Authors	Year	Country	Species	Tissue	Mean	Range
7	Anonymous	1972	? Atlantic Ocean	Zooplankton		1.50	
19	Risebrough *et al.*	1972	USA, Atlantic Ocean	Zooplankton	Lipid extract	40.00	(median)
20	Veith *et al.*	1977	USA, W. Lake Superior	Zooplankton		0.10	
21	Giam *et al.*	1973	Mexico, Gulf of Mexico & N. Caribbean	Zooplankton			<0.003–1.055
8	Holden,	1970	Scotland	Zooplankton		0.03	
22	Linko *et al.*	1974	Finland, Turku archipelago		Lipid extract	25.00	
23	Ware & Addison	1973	Gulf of St. Lawrence	Plankton		0.19	0.090–3.00
9	Falkmer *et al.*	1977	Sweden, Gullmar fjord	Atlantic hagfish	Liver	5.00	
		1977		Open sea hagfish	Liver	0.20	
10	Holden	1973	Scotland ('69–'71)	Mussels from unpolluted			0.03–0.067
				and polluted areas			0.017–1.70
13	Raluja *et al.*	1973	Spain				0.58–1.36
11	Claeys *et al.*	1975	USA, Oregon coast estuaries	Bivalve mollusks		<0.003	
			Oregon-Washington coast	Pink shrimp		0.008	
			Oregon-Washington coast	Euphausiids		0.025	
12	Duke *et al.*	1970	USA, Escambia Bay, FL.	Shrimp and crab			up to 7.00
24	Bowes *et al.*	1973	USA, San Miguel Island, CA.	Sea lions	Blubber	62.00	
					Liver	3.00	
25	Buhler *et al.*	1975	USA, The central Oregon coast	Sea lions	Blubber		21.20–34.10
18	Addison *et al.*	1973	Canada, Gulf St. Lawrence	Harp seals			3.0–22.0
14	Addison & Brodie	1977	Canada, Gulf St. Lawrence	Grey seals	Blubber lipid	14.50	
					Milk lipid	60.00	
15	Holden	1972	England, The Baltic, North & Irish Seas	Seals	Blubber	212.00	
26	Helle *et al.*	1976	Finland	Ringed seals—pregnent	Blubber	56.00	
				Ringed nonpregnant	Blubber	77.00	
27	Snachenbrecker	1973	Canada, Atlantic coast	N. Am. Fin-back whales	Blubber		0.012–0.185



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TABLE 1 (*continued*)

PCB RESIDUES IN MARINE ORGANISMS

Ref	Authors	Year	Country	Species	Tissue	Mean	Range
17	Gaskin *et al*	1974	Lesser Antilles	Cetaceans: Short-finned pilot whales and long snouted dolphin	Blubber		2.69 5.00
16	Tatsuki *et al*	1975	Canada	Cetaceans and dolphins	Blubber		0.70 147.00
28	Zitko & Hutzinger	1972	Canada & USA, Gulf of Maine, Bay of Fundy	Basking shark	Muscle	0.07	
				White shark	Liver	218.00	
29	Jensen *et al*	1969	Sweden	11 marine species			0.019 15.0

TABLE 2

PCB RESIDUES IN FISH (ppm)

Ref	Author	Year	Country	Species	Mean	Range
40	Anonymous	1971	USA, Alabama	Fish		up to 360.0
31	Carr	1972	USA, The Ohio shore of Lake Erie	Different species of fish		0.08 4.40
30	Bubles & Cleys	1972	USA, Eastern rivers	Different species of fish		up to 140.0
39	Bache *et al*	1972	USA, Cayuga lake, Ithaca	A 12-year-old trout	26.0	
41	Smith *et al*	1974	USA, Utah	Different species of fish		0.05 0.97
32	Haile *et al*	1975	USA, Lake Ontario	Different species of fish	5.15	
11	Cleys *et al*	1975	USA, Columbia river, Rogue river	Selected fish species	0.480	
				Summer-run steel head	0.125	
34	Parejko *et al*	1975	USA, Lake Superior ('71)	Lake trout	7.00	
33	Veith	1975	USA, Lake Michigan ('71)	13 Species-rainbow smelt -Lake trout	2.7 15.0	lowest average highest average

20	Veith *et al*	1977	USA, West Lake superior ('72 '73)	Fish	0.1	
42	Baird *et al*	1975	Mexico, Gulf	Larger fish	5.0	
				17 Species of mesopelagic fishes		up to 0.02
28	Zitko & Hutzinger	1972	Canada, Nova Scotia & New Brunswick	Marine fish		0.2 0.5
43	Zitko	1972	USA Canada, Nova Scotia & New Brunswick	Fresh-water fish		2.1 10.0
				American eel, herring, Atlantic Salmon		0.3 0.7
44	Sims *et al*	1975	Canada, Atlantic coast ('71)	Cod liver		3.4 23.3
37	Duguchi *et al*	1971	Japan, Tokyo Bay	Sardines		
45	Bjerk & Sundby	1970	Norway	Dogfish		1.0 10.0
				Pike	0.03	
46	Bjerk	1972	Norway, Coastal waters Oslo harbor	Sprat	0.04	
				Herring		up to 3.4
18	Hauge	1972	Norway			up to 16.0 (fat bass)
47	Linko *et al*	1974	Finland, the Turku archipelago	Sea fishes		0.01 3.0
				Baltic herring	0.31	
48	Jensen *et al*	1973	Finland	Pike	0.05	
				Pike (Ovaries)	190.0	
				Herring	16.0	
8	Holden	1970	Scotland			1.8 110.0 (fat bass)
				Clupeoid fish	2.60	
36	Monod *et al*	1971	France, Bay of Marseilles	Fresh water fish	0.00	
49	Eichner	1973	Germany, Lake Constance, Tribut. of the Rhine	Sardines		0.7 5.1
				White fish perch		0.01 1.2
50	Hueckenbeth	1973	Germany, North Sea	Roak, trout		0.05 3.9
				Lean fish	0.2	
35	Viviani *et al*	1971	Adriatic Sea	Fat fish	1.3	
				Anchovies		0.18 0.96
				Sardines		0.37 1.06
13	Baluja *et al*	1973	Spain, Mediterranean coast Atlantic	Sprats		0.62 0.92
				Sardines		0.34 0.40
				Sardines		0.34 0.40

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Deep-sea fish have relatively low PCB residue levels; 0.2–0.5 ppm PCBs were found in marine fish in Canada[28] and 0.1–3.0 ppm in fish from Norwegian seas.[28]

PCBs residue values in fish varied with the species. Different species of fish caught off the Ohio shore of Lake Erie (yellow perch, coho salmon, carp, channel catfish, fresh water drum, and white brass) showed a range with average PCB residues of 0.08 to 4.40 ppm. Significantly higher levels were found in channel catfish.[31] From 13 species of fish sampled from Lake Michigan, the rainbow smelts had the lowest average of 2.7 ppm and the lake trout the highest, 15.0 ppm.[33]

PCB residue levels were higher in larger fish. Most trout and salmon from Lake Michigan longer than 12 inches, contained PCB levels higher than 5.0 ppm, which is the tolerance level established by FDA.[34] Larger fish from Lake Superior had a residue level of PCBs of 5.0 ppm, in comparison to smaller fish whose PCB residue level was 1.0 ppm.[29] A 12-year-old trout was reported with 26.0 ppm PCBs.[29]

PCB Residues in Birds (Tables 3 and 4)

The avian species accumulated the highest PCB residues. They constitute the top of the most affected and therefore the most studied food chain.

PCB residue levels in birds are very high in those regions of industrialized countries where industrial wastes are disposed of via fresh waters and coastal waters.

PCB residues in the adipose tissue of birds vary from several ppm to hundreds and even thousands of ppm. Amongst the birds of the USA, White-tailed eagles were reported to have a PCB residue level of 14,000.0 ppm, peregrine falcons 2,000.0 ppm[31] and herons 900.0 ppm.[32] Common murres, found dead, had 4,000.0 ppm in the brain.[33] Chacalacas fed on unsprayed native fruits had comparatively very low adipose-tissue, PCB-residue levels of 0.17 ppm.[34]

English fresh-water fish-feeding birds had liver PCB residue levels of up to 900.0 ppm,[35] and gannets of the eastern and western coasts of England had a liver PCBs residue range of 4,720.0–9,590.0 ppm,[36] while terrestrial predatory birds had liver PCB residues in the range of only 1.3–272.0 ppm.[37] High levels of PCBs in the birds of Germany, 24.0–740.0 ppm,[38] and much lower levels, 5.0–6.2 ppm, in terrestrial and aquatic avian species of Spain[39] were reported.

Adult merlins were shown to have a residue level of 196.0 ppm as against immature merlins with only 28.6 ppm.[40]

Guillemots found dead had higher liver residue levels, 50.0 ppm, than shot guillemots, 0.5 ppm.[41] Experimentally in cormorants, death occurred at a total body burden similar to that found in cormorants found dead naturally.[42]

Reduction of avian populations, as an effect of PCBs, occurs because of the excessively high residue levels in birds and their eggs, as a result of neurologic changes induced by PCBs (changes that reduce the defensive fitness, the birds becoming easy prey for predators), of immunologic changes that render the birds more susceptible to infectious diseases, and because of a reduction of reproduction success. Some of these negative effects of PCBs may be potentiated by one or another of the xenobiotics that abound in the current environment.

PCB Residues in Avian Eggs (Table 5)

The eggs of fish-eating birds have the highest residue levels of PCBs. The average for PCB residues in egg-extracted lipids of 13 species of fish-eating birds of the Upper Great Lake States was 339.7 ppm. Partial averages for the PCB residues of the eggs of

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TABLE 3

PCB RESIDUES IN BIRDS OF NORTH AMERICA (ppm)

Ref.	Author	Year	Country	Species	Tissue	Mean	Range
51	Gustafson	1970	USA	Peregrine falcons		2900.00	
				White-tailed eagles		14000.00	
52	Anonymous	1970	?	Herons		900.00	
60	Risebrough *et al.*	1970	USA, Western shore of Lake Michigan ('68-'69)	Young peregrine falcons	Adipose	52.50	
				Adult merlins		196.00	
				Immature merlins		28.60	
63	Anonymous	1971	USA, Long Island Sound	Terns	Breast muscle		5.00-175.00
64	Hays & Risebrough	1972	USA, Great Gull Island, NY ('69-'70)	Abnormal young terns	Breast muscle	25.00	
				Fish brought by adult birds		1.00	
65	Belisle *et al.*	1972	USA	Bald eagles (one)	Brain	235.0	
66	Mclane *et al.*	1973	USA, (11 states)	Woodcock wings	Whole bird extr. lipid		4.27-8.63
67	Creichus *et al.*	1973	USA, S. Dakota (Lake Poinsett)	Pelicans	Adipose	22.40	
68	Fisher	1973	USA, N. Pacific ('69)	Birds	Adipose	15.30	
69	Dacre	1974	USA	Mutton birds of New Zealand	Adipose	1.83	
70	Kreitzer	1974	USA, several states ('70-'71)	Mourning dove	Breast muscle	0.12	
53	Scott *et al.*	1975	USA, Oregon coast ('69)	Common murres	Brain	4000.00	dead birds
			('69)			3700.00	during
			('70)			1100.00	die-off
71	Cromartie *et al.*	1975	USA, (18 states) ('71)	Bald eagles	Carcasses		0.30-290.00
					Brain		0.10-150.00
			('72)		Carcasses		0.60-1200.00
					Brain		0.65-190.00
54	Marinn	1976	USA, South Texas, Rio Grande	Chacalacas	Adipose	0.17	
72	Zitko *et al.*	1972	Canada, Bay of Fundy	Herring gulls	Adipose	1.40	Aroclor 1460
78	Zitko and Hutzinger	1972	Canada and USA	Double crested cormorant	Breast muscle	3.38	

TABLE 4

PCB RESIDUES IN BIRDS OF EUROPE (ppm)

Ref.	Authors	Year	Country	Species	Tissue	Mean, range
45	Bjerk and Sundby	1970	Norway	Starling	Breast muscle	0.014
38	Hauge	1972	Norway	Carnivorous birds	Breast muscle	3.00
73	Odsjö	1973	Sweden, S.E. Coast	Eagle owls (found dead)	Brain	260.00
					Breast muscle	110.00
74	Bogan and Bourne	1972	Scotland-Arctic	Large gulls and skuas	Muscle & liver	535.00
55	Prestt *et al.*	1970	England ('68)	Fresh water fish-feeding birds	Liver	up to 900.00
				Bird-feeding raptors	Liver	up to 70.00
61	Parslow & Jefferies	1973	England, Irish Sea area	Guillemots I dead	Carcasses	3.00
					Liver	50.00
				II shot	Carcasses	1.00
					Liver	0.53
56	Parslow *et al.*	1973	England, E. & W. coasts	Gannets	Liver	4720.00-9570.00
57	Karlog *et al.*	1971	Denmark & Greenland	Terrestrial predatory birds	Liver	1.30-272.00
75	Braestrup *et al.*	1974	Denmark & W. coast of Greenland	Ducks and purple sandpipers	Adipose	1.20-3.30
				Ptarmigans and Bunnich's guillemots		10.10-12.90
				Cormorants and ravens		26.30-37.10
76	Koeman *et al.*	1972	The Netherlands	Dead cormorants	Brain	190.00
					Liver	319.00
67	Koeman *et al.*	1973	The Netherlands	Dead cormorants; Total of Nestling cormorants	Carcasses	0.50-1.0 g
					Brain	0.69
58	Acker & Schulte	1971	Germany	Long eared owls, sparrows, hawks, falcons	Adipose	24.00-740.00
77	Figge *et al.*	1976	Germany	Birds from N. Germany		2.20 (T. DDT + PCBs)
59	Baluja *et al.*	1974	Spain	Terrestrial and aquatic species		5.00-6.20

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these birds species showed species differences. The eggs of herring gulls had a PCB residue average of 2224.5 ppm (on a fat basis) and the red-necked grebe eggs an average of 744.6 ppm (on a fat basis). The average residue level of PCBs for egg-extracted lipids from fish-eating birds of Louisiana was only 35.0 ppm. Signs of eggshell thinning were found in 9 out of 13 species in the Upper Great Lake States and in 2 out of 7 species in Louisiana.[78] Eggs of the bald eagle had the lowest PCB residue levels in Alaska, 2.2 and 1.1 ppm (wet weight) and the highest in the state of Michigan, 300 ppm, in a survey made during 1969–1970.[79] In 1973 in Ontario, a level of 434 ppm was reported.[80]

PCB levels of eggs of the brown pelican were 1.0–11.0 ppm (wet weight), during 1970.[81] These levels showed a continuous decrease over the following years, reaching an average of 4.7 ppm in 1973, when for the first time in many years the brown pelican reproduced well.[82] Wet-weight, egg PCB-residue levels of the double crested cormorant averaged 45.6[83] and 43.5 ppm.[84]

Birds of industrialized areas have higher egg PCB residue levels in comparison to birds of nonindustrialized areas, 3.34 ppm versus 1.02 ppm.[85] Another example of this situation is a study carried out in Germany during 1974–1976 on eggs of 19 native species. A range of 2.0 to 847.0 ppm PCB residue levels was reported, with higher contamination in eggs from industrialized areas of the Ruhr and Nürenberg.[86]

White-tailed eagles of the Gulf of Bothnia showed high PCBs contamination with egg residue levels averaging 157.0 ppm. Reproduction failures in these birds have been reported.[87] In Schleswig-Holstein, Germany, PCB residue levels in eggs from white-tailed eagles ranged from 6.1 ppm to 97.0 ppm. Here, the PCB levels have not been definitely correlated with a low reproductive rate.[88]

In northern Europe, guillemots,[79] ospreys,[87] eiders,[89] pochards,[85] and sparrow hawks[90] showed relatively high egg PCB residue levels, 16.0, 25.0, 35.0, 40.7, and 47.0 ppm, respectively. Eiders from a protected island of Denmark, were reported to have substantially decreased their PCB residue levels, from 35.0 ppm to 14.0 ppm, in a two-year period.[89]

The effort to reduce the contamination of rivers, lakes and costal waters by PCBs and other organochlorine pollutants, will result in lower egg xenobiotic residues and will prevent the upsetting of the biologic equilibrium in nature.

PCB Residues in Terrestrial Animals (Table 6).

PCB residues were found in terrestrial living beings in different concentrations, from the smallest, at the limit of detection, 0.01 ppm, in adipose tissue of herbivorous mammals in Sweden[77] to thousands of ppm in fish-eating birds.[91]

PCBs are current constituents of living beings in our epoch. They have been reported in the polar bear at less than 400 miles from the North Pole[92] and in every species sampled throughout the earth.

In nursing cows and newborn pups, in the USA (PA), 5.8 and 5.5 ppm PCBs respectively, were found in the adipose tissue. In 2-month-old pups an average of 33.0 ppm was reported, perhaps due to the milk content of PCBs.[93] In minks, the PCB residues were among the highest found in terrestrial mammals, 45.0 ppm in the adipose tissue. The high levels were presumably due to a fish diet.[73] Dead minks found in 1969–1970 in New England, had 73 times the level of PCBs found in healthy minks in 1974. The authors of the report do not think that the high level of PCBs found in the carcasses were responsible for the death of the animals.[94] In hares and foxes in Germany, relatively small PCB residue levels were found in their adipose tissue, an

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TABLE 5

PCB RESIDUES IN EGGS (MEAN, RANGE-ppm)

Ref.	Authors	Year	Country	Bird species	Wet weight	Lipids
			In North America			
91	Gress *et al.*	1971	USA, Farallon islands	Common murre		165.0
81	Blus *et al.*	1971	USA	Brown pelican	<1.0 11.0	
19	Wiemeyer *et al.*	1972	USA, Alaska-Kodiak ('69)	Bald eagle	2.2	
			"Admiral. Isl ('70)		1.1	
			Maine ('69)		9.9	
			Minnesota ('69-'70)		7.7	
			Florida ('69)		12.2	
			Michigan ('69)		27.7	
74	Brown *et al.*	1973	USA	Herring gull	300.0	
78	Faber & Hickey	1973	USA, Upper Great Lake States	Fish-eating birds		339.7
				Red necked grebe		744.6
				Common merganser		260.2
				Red crested merganser		469.0
				Herring gull		2224.5
			Louisiana	Fish-eating birds		35.0
82	Blus *et al.*	1977	USA, South Carolina ('70)	Brown pelican	6.1	5.0 74.5
			('71)		5.2	3.9 70.4
			('71)		6.5	1.5 36.5
			('72)		7.5	2.6 32.3
			('73)		4.7	0.9 19.3
80	Grier	1977	USA, N. East & Ontario ('66-'73)	Bald eagle	434.0	
92	Longcore & Mulhern	1973	USA, N. East & Canada ('71)	Black duck	3.30	1.0 6.90
					<0.05	0.02 0.05
83	Zitko	1972	Canada, New Brunswick	Double crested cormorant	45.6	
				Gull	7.4	
84	Zitko & Choi	1972	Canada, New Brunswick	Double crested cormorant	43.5	
72	Zitko *et al.*	1972	Canada, Bay of Fundy	Herring gull	0.1	(Aroclor 5460)
93	Mes *et al.*	1974	Canada, Bay of Fundy	Chicken	<0.010	
			In Europe			
94	Bjerk and Holt	1971	Norway	Herring gull		0.2 38.0
				Common gull		trace 0.8
29	Jensen *et al.*	1969	Sweden, Baltic	Guillemot	16.0	
87	Koivusaari *et al.*	1972	Finland, Quarken area Gulf of Bothnia ('70-'71)	Osprey	25.0	
89	Fog & Kraul	1973	Denmark (from a protec- island)	White tailed eagle	157.0	
85	Block & Kraul	1972	Denmark (collected from two localities)	Eider '70	35.0	
				'72	14.0	
				Swan	1.02	
					3.34	Industrial areas
				Pochard	40.70	
90	Koeman *et al.*	1972	The Netherlands (east)	Sparrow hawk '69 '71	47.0	
88	Koeman *et al.*	1972	Germany-Schleswig-Holstein	White-tailed eagle		6.1 97.0
86	Conrad	1977	Germany-Schleswig-Holstein	19 Native bird species '74-'76		2.0 847.0
95	Mestres & Iller	1973	France	Gull	0.8	23.0 PCTs

TABLE 6

PCB RESIDUES IN TERRESTRIAL ANIMALS (ppm)

Ref.	Authors	Year	Country	Species	Tissue	Mean	Range
96	Anonymous	1972	?	Polar bears, present (Less than 400 miles from North Pole)			
98	Friedman *et al.*	1977	USA (New England)	Minks (found dead) '69-'70		73-fold higher levels than in healthy minks in 1974	
97	Kurts & Kim	1977	USA	Cows (nursing)	Adipose	5.8	
				(newborn)		5.5	
				(2-month-old pups)		33.0 (3.4 ppm plasma level was found in 2 month-old pups)	
73	Odsjö	1973	Sweden	Herbivorous mammals		0.01 (at the limit of detection)	
				American minks	Muscle	0.58	
					Adipose	45.00	
99	Bruggemann	1974	Germany	Hares	Adipose	0.22 (in 20 out of 72 samples)	
100	Hidaka *et al.*	1972	Japan, Lake Biwa	Foxes	Adipose	2.50 (in 1 out of 5 samples)	
				Corbiculae '63	(preserved)		0.04 2.4
				'71			0.06 1.1

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average of 0.22 ppm PCBs in 20 positive out of 72 samples in hares and 2.50 ppm in the adipose tissue of 1 positive out of 5 samples of adipose tissue of foxes.[79]

PCB Residues in the Adipose Tissue of the General Population (Table 7)

PCB average residues in the adipose tissue of groups of the general population from different countries of Europe, range from about 1.0 ppm to several ppm. The lowest levels are reported from the Northern countries: Norway 0.90 ppm, the Oslo area 0.80 ppm,[101] England[102] and The Netherlands[103] up to 1.0 ppm and Finland with an average of 1.97 ppm.[100] Austria had a higher average for the adipose tissue PCB residue levels, 3.5 ppm, with a range of 0.3–7.3 ppm.[105] Germany had the highest level of PCB residues in the general population with a range of averages from 6.8 ppm in Cologne to 10.0 ppm in Munich.[106]

From the USA, several surveys[96,103,106] reported in 1972 showed that the majority of cases (57.6–68.9% of the cases studied) had an adipose tissue PCBs residue level of less than 1.0 ppm, about a third (25.9–36.7%) had PCB residue levels ranging from 1.0 to 2.0 ppm and only 5.2 to 7.6% of cases had residue levels of over 2.0 ppm. A study of the EPA's Perrine laboratory, FL., found PCBs residue levels ranging from 1.0 to 6.0 ppm, but as much as 600 ppm has been found.[96]

In Japan where the storage of PCBs in man has been extensively studied, averages of less than 1.0 ppm, 0.6 ppm,[109] 0.8 ppm,[110] and 0.9 ppm[111] were reported during 1973 and 1974, but at the same time, averages of several ppm were also found: 5.0 ppm,[112] 2.86 ppm,[113] and 2.6 ppm.[114]

The studies carried out in Germany show a tendency for PCB residues of the general population to increase during the years 1970 to 1974: 5.7 ppm for 1970,[115] 6.4 ppm for 1971,[36] and 8.3 ppm for 1974[116] having been reported. Such a tendency cannot be refuted for other countries since annual reports are very few: Inoue *et al.*, reported in Japan 1.60 ppm for 1974 and 2.60 ppm for 1975.[116,117]

PCB levels according to sex, showed higher values in males.[118]

PCB Plasma Residues in Man (Table 8).

Plasma PCB residues were studied especially in Japan because of the accidental poisoning of humans that occurred in 1968. Plasma PCB residue levels ranged from several ppb to tens of ppb, in the general population of those countries where the sampling was performed. The Yusho patients presented high adipose tissue and plasma residue levels during the 1–3 years after the alimentary poisoning took place. In recent years PCB plasma levels have dropped to almost the levels found in the general population. Yet, there remains for those Yusho cases with PCB levels towards the upper range of plasma values, a specific gas chromatographic pattern: peak 17 was higher and peak 13 was lower as compared with the controls.[126–128] Besides, 7 years after the accident, very high levels may still be found in several Yusho patients, with 92.0 and 230.0 ppb being reported in two patients.[114]

Occupationally exposed people have rather high plasma PCB residue levels: 75.0–1900.0 ppb plasma PCBs were reported in persons working in a capacitor plant in Finland,[127] and 100.0–650.0 ppb in a capacitor plant in Japan. Plasma PCB levels of 90.0–740.0 ppb were found in these workers one month after exposure.[129] Skin lesions were reported.[129]

Increased plasma levels of PCBs occurred also in cachectic patients and in starved animals.

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TABLE 7

PCB RESIDUES IN THE GENERAL POPULATION (ADIPOSE TISSUE, ppm)

Ref.	Authors	Year	Country	Wet tissue	(mean, range)
101	Bjerk	1972	Norway	0.90	
			Oslo area	0.80	
102	Abbott *et al.*	1972	England		
104	Hattula *et al.*	1976	Finland, Puri Iyvaskyla	1.97	
103	Freudenthal & Greve	1973	The Netherlands		≤1.0
115	Acker & Schulte	1970	Germany	5.7	
58	Acker & Schulte	1971	Germany	6.4	≤1.0
116	Acker & Schulte	1974	Germany	8.3	4.3 9.3
106	Acker & Schulte	1974	Germany, Cologne	6.8	
			Germany, Götigen	7.5	
			Germany, Hamburg	7.9	
			Germany, Berlin	9.1	
			Germany, Munich	10.0	
105	Pesendorfer *et al.*	1973	Austria, Vienna	3.5	
40	EPA's Perrine Lab (FL)	1971	Austria, Vienna		0.3-7.3
96	Anonymous	1972	Austria, Vienna	29.7% popn.	1.0 6.0
			Austria, Vienna	7.6% popn.	1.0-2.0
107	Price and Welch	1972	Austria, Vienna	57.6% popn.	2.0
			Austria, Vienna	36.7% popn.	≤1.0
			Austria, Vienna	5.6% popn.	1.0-2.0
108	Yobs	1972	USA	68.9% popn.	>2.0
			USA	25.9% popn.	≤1.0
			USA	5.2% popn.	1.0-2.0
					2.0

TABLE 7 (*continued*)

PCB RESIDUES IN THE GENERAL POPULATION (ADIPOSE TISSUE, ppm)

Ref.	Authors	Year	Country	Wet tissue	(mean, range)
119	Wassermann *et al.*	1973	Israel	2.75	
112	Ui	1972	Japan	5.0	
113	Nishimoto *et al.*	1972	Japan, Kochi, Kyoto	2.86	≤7.5
120	Mizutani	1972	Japan	4.7	
110	Curley *et al.*	1973	Japan	0.8	0.3 1.8
121	Doguchi	1973	Japan	5.1	(M 70 79 year)
			Japan	2.4	(F 60 69 year)
			Japan	0.6	0.1 2.1
109	Doguchi *et al*	1974	Japan	0.9	0.3 1.9
111	Masuda & Kagawa,	1974	Japan, Saga ('70)	1.6	
117	Inoue *et al*	1974	Japan	2.6	
114	Inoue *et al.*	1975	Japan	2.01 (M)	1.1 PCTs
118	Fukano & Doguchi	1977	Japan	0.59 (F)	1.04 PCTs
122	Solly & Shanks	1974	New Zealand	0.82	
123	Dyment *et al.*	1971	New Guinea	Absent	

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TABLE 6

PCB RESIDUES IN MAN (mean, range)

Ref.	Authors	Year	Country	General Population (plasma levels-ppb)				Cases	
127	Karppanen & Koiho	1973	Finland		3.1-	12.0			
132	Finklea *et al.*	1972	USA, Charleston		-	29.0		723	Volunteers
131	Polishuk *et al.*	1977	Israel	19.3					Pregnant women
124	Inoue *et al.*	1973	Japan	3.3			4.5 (urban) 2.7 (rural)	42	
117	Inoue *et al.*	1974	Japan	4.9					
125	Masuda *et al.*	1974	Japan	3.0				37	
126	Okumura *et al.*	1974	Japan	2.8				37	
134	Yukamatsu *et al.*	1974	Japan		1.0-	7.0		82	
135	Doguchi & Fukano	1975	Japan	3.2			5.0 PCTs		
118	Fukano & Doguchi	1977	Japan ('73)		2.2-	5.1	0.7-19.6 PCTs		
			Japan ('75)		1.8-	3.8	1.1-9.4 PCTs		
			Occupationally Exposed Persons (plasma levels-ppb)						
127	Karppanen & Koiho	1973	Finland		36.0-	63.0	(in an analytic lab)		
					75.0-	1900.0	(in a capacitor plant)		
128	Hasegawa *et al.*	1972	Japan		100.0-	650.0	(in a capacitor plant)		
					90.0-	740.0	(1 month after exposure)		
136	Kitamura *et al.*	1973	Japan	800.0			(in an electric condenser plant, 1 month after exposure)		
				300.0			(in an electric condenser plant, 3 months after exposure)		
			Yusho Patients						
137	Yamaguchi *et al.*	1971	Japan ('69)	75.5			(adipose tissue-ppm)		
112	Ui	1972	Japan	13.0			(adipose tissue-ppm)		
138	Masuda & Kagawa	1974	Japan ('69-'72)	2.5	0.7-	4.3	(adipose tissue-ppm)		
124	Inoue *et al.*	1973	Japan ('73)	7.0	2.0-	15.0	(plasma-ppb)		
125	Masuda *et al.*	1974	Japan ('73)	7.0			(plasma-ppb)	41	
126	Okumura *et al.*	1974	Japan	8.6			(plasma-ppb)		Yusho UGC pattern
				3.8			(plasma-ppb)		Intermediate pattern
134	Takamatsu *et al.*	1974	Japan		2.0-	15.0	(plasma-ppb)	32	
114	Inoue *et al.*	1975	Japan ('75)	6.1			(plasma-ppb)		
			Severe Wasting Diseases (blood-ppm)						
129	Hesselberg and Scherr	1974	USA	47.0					



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In patients with severe wasting diseases, 47.0 ppm PCBs was reported in venous blood.[128] An increase in the death of female eiders, at the end of the physiologic starvation that occurs during the breeding cycle, was explained by the release of OCC residues during the using up of stored body fat.[129] In rats, starved during the recovery from the effects of Kanechlor-400 or Kanechlor-500 given previously, there was a temporary but definite shortening of hexobarbital sleeping time, suggesting the possibility of PCB release from the adipose tissue deposits.[130]

PCB Residues in Human Milk (Table 9)

The average PCB residue levels in human milk have been reported for several countries of Europe, North America and Asia. These averages vary from ten ppb in Norway,[108] to about a hundred ppb in Germany.[115]

PCB residues in human milk were higher than those found in colostrum, 74.5 ppb[139] versus 44.3 ppb.[133]

For milk and colostrum the individual chlorinated biphenyl compounds showed different percentages of the total PCB value found, peaks 9, 13, and 14 representing higher percentages in colostrum, whereas peaks 2, 3, 4, and 6 showed higher percentages in milk collected during the third through the fifth month of nursing.[139]

Smaller concentrations of PCBs were excreted in milk in overweight women and in women over 30 years old as compared to normal or underweight women and to women under 30 years of age.[133]

Although the excretion of PCBs and other xenobiotics in milk represent an efficient means for their removal from the female body it should be remembered that these compounds are transferred with the milk to the infant.

Because of the great range of milk PCB residues, due to differences in exposure and biochemical individuality, it is obvious that special care for the nutrition and environment of potential mothers will lower the xenobiotic content of the human female body and consequently, the placental and milk xenobiotics transfer to the fetus and infant will be decreased.

Effects of PCBs on Reproduction in Aquatic Organisms (Table 10)

PCBs are toxic to some aquatic organisms at concentrations existing presently in sea water. Phytotoxicity occurred at levels less than 5 ppb.[133] Selective toxicity of PCBs for phytoplankton communities was reported. Netplankton production was inhibited by more than 50% by Aroclor 1242 at levels of 10 and 25 ppb, while nannoplankton (which contributes about 73% to the entire phytoplankton production) was not affected.[193] Reduction of phytoplankton division in media containing PCBs was also reported.[154,155] This selective toxicity for phytoplankton species may affect marine herbivorous populations.

At a concentration of 21 ppb Aroclor 1254 in sea water, a decrease in mating occurred in *Gammarus oceanicus*. The decrease seems to be the result of toxic effects in males.[156]

Premature hatching and decrease in hatchability as well as decreased survival and growth in the young fish were observed when coho salmon eggs were kept in Aroclor-containing media.[157]

A diminished percentage of pregnant females was noted in marine mammals. Pregnant Ringed seals, caught in the Bosnian Bay, Choska Inlet, and Ochotskan Sea,

TABLE 9

PCB RESIDUES IN HUMAN MILK (mean, range)

Ref.	Author	Year	Country	Whole milk (ppb)	Milk-extracted Lipids (ppm)
115	Acker & Schulte	1970	Germany	103.0	3.5
58	Acker & Schulte	1971	Germany		5.3
140	Knoll & Jayaraman	1973	Germany	90.0	
141	Pesendorfer	1975	Austria, Vienna		1.54
			Mistelbach		1.29
142	Jaszkiewicz *et al.*	1975	Poland	9.0	0.01 1.40
143	Eulandyk	1977	Poland	390.0	
144	Westöö *et al.*	1970	Sweden	16.0	
145	Westöö & Norén	1972	Sweden (1967)	14.0	
			Sweden (1971–1972)	25.0	
146	Westöö	1974	Sweden	Increased	
101	Bjerk	1972	Norway	10.0	
147	Risebrough & Brodine	1969	USA, California	60.0	
123	Dyment *et al.*	1971	USA, Texas	Absent	
			New Guinea	Absent	
148	Savage *et al.*	1973	USA, Colorado, rural		40.0 100.0
149	Strassman & Kutz	1975	Arkansas & Mississippi		Trace
150	Musial *et al.*	1974	Canada, New Brunswick	22.0	15.3
			Canada, Nova Scotia	18.0	18.6
133	Polishuk *et al.*	1977	Israel	44.3	(colostrum) 3.10
139	Miller *et al.*	1978	Israel	74.5	2.29
151	Oura *et al.*	1972	Japan, Toyama	30.0	1.10
152	Hidaka *et al.*	1972	Japan, Kyoto	50.0	
113	Nishimoto	1972	Japan, Kochi & Nangoku	30.0	
111	Masuda & Kagawa	1974	Japan, Fukuoka (Jan.–Mar. '72)	30.0	10.0- 60.0 1.2 0.10- 5.6
			Japan, Ishigaki (Mar. '72)	14.0	10.0- 20.0 0.4 0.10- 0.7

TABLE 10

EFFECTS OF PCBs ON REPRODUCTION IN AQUATIC ORGANISMS

Ref.	Authors	Year	Species	Compound, dosage	Effect
155	Morgan	1972	Chlamidomonas	Aroclor	Decreased cell density. Dose-related decrease in uptake of ^{14}C.
153	Moore	1973	Phytoplankton	Aroclor 1242 10 & 25 ppb	Net plankton production was inhibited > 50%. Nannoplankton was not inhibited
154	Fisher	1975	Phytoplankton	PCBs	Reduction of cell division rate.
159	French	1976	Flagellated protoroan	Aroclor 10.5 ppm DDT 425.0	50% depression of cell population growth 50% depression of cell population growth.
160	Maki & Johnson	1975	Daphnia magna Strauss	PCBs 19.0 ppb	50% reduction in the number of young
156	Wildish	1972	*Gammarus oceanicus*	Aroclor 1254 10 & 100 ppm in sea water/10 hr.	Survival and development were hindered in the embryos.
				Aroclor 1254 21.0 ppb	Decrease in mating.
157	Halter & Johnson	1974	Eggs of Coho Salmon	Aroclor 1254 4.4 ppb until 4 w. after hatch. 15.0 ppb until 2 d. before hatching	Decrease of egg hatchability, premature hatching and decreased survival and growth in the young fishes.
161	De Lang *et al.*	1973	Sea lions of S. California	Naturally exposed	A high rate of premature births in those with higher levels of PCBs.
26	Helle *et al.*	1976	Ringed seals from: Bosnian bay Choska inlet Ochotskan Sea	Naturally exposed	Pregnant seals had lower PCB and DDT residue levels. About half of the non-pregnant population showed evidence of implantations followed by resorption or abortion
158	Helle *et al.*	1976	Seals, Gulf of Bothnia	Naturally exposed	Only 30% were pregnant. The nonpregnant seals had higher PCB and DDT residues They presented uterine changes.

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Finland, were shown to have lower organochlorine residues (75 ppm DDT and 56 ppm PCBs) as compared with a nonpregnant population (130 ppm DDT and 77 ppm PCBs). About half of the nonpregnant population showed signs of implantation.[26] Seals from the Gulf of Bothnia presented a 30% pregnancy rate (which is considered as a low rate). The nonpregnant seals had higher organochlorine residues.[180]

Effects of PCBs on Reproduction in Birds (Table II)

Decrease in the reproduction success in birds is the most striking effect of the ever-increasing environmental chemical pollution of the last decades. It is the result of diminished egg production, eggshell thinning and increased rate of embryonic mortality. The reproductive success for sparrow-hawk eggs collected in east Netherlands during 1969–1971 was approximately 25% lower than in the period 1931–1943. PCBs and DDT residues were 47 and 26 ppm respectively.[182]

Impaired egg production and decline in eggshell parameters were correlated with increased xenobiotic residues (OCC: DDT, dieldrin, PCBs and such heavy metals as mercury and cadmium) in several avian species.[76]

Inhibition of ovulation was reproduced experimentally in birds given PCBs.[103]

Eggshell thinning was reproduced experimentally with PCBs in several avian species. The eggs of Japanese quail given 50 ppm PCBs in their diet for 15 weeks presented a decreased eggshell thickness (4.5%) and an increased percentage of cracked eggs.[164,165] High levels of DDT and DDE (100 and 200 ppm) given to Japanese quail (about 500 and 600 ppm residues in their eggs) produced a 5% decrease in the shell thickness and consequently an increased shell breakage in the eggs of these birds. At this level, the activity of carbonic anhydrase in the shell glands was decreased by 12–15%.[164] Eggshell thinning was also reproduced in chickens given Aroclor 1254 or 1242[166] but not in ring doves given 100 ppm Aroclor 1254 for 3 months,[167,169] or in white Leghorn chickens and Japanese quail given 10 and 20 ppm PCBs.[166] These negative results seem to be due at least in some cases to inadequate dosage, since the Japanese quail egg thickness was affected by larger doses of PCBs as mentioned above.

Eggshell thinning, occurring in nature, has often been attributed to other environmental pollutants rather than to PCBs. The fact that eggshell thinning was reproduced experimentally with PCBs suggests that the responsibility for such eggshell thinning in nature may be shared by many xenobiotics among which the most frequently cited were DDT, dieldrin, PCBs, and mercury.

Normal eggshell production depends on the plasma estrogen levels and the activity of carbonic anhydrase in the shell gland. Chlorinated hydrocarbons activate normally dormant hydroxylases in the liver, which enhance the hydroxylation of the steroid estrogen rings, resulting in lower estrogen levels.[170] PCBs are more potent activators of estrogen degradation than are DDT and DDE.[51] The lower estrogen levels result in a lower supply of calcium to the oviduct and contribute thus to eggshell thinning.[170] Calcium carbonate is produced from bicarbonate and calcium in the presence of carbonic anydrase.

Reduction in hatchability due to embryonic mortality was reproduced experimentally in mallards,[171] in Leghorn chickens,[172] in ring doves,[167] in pheasants,[173,174] in chickens[166] and in hens.[175]

PCBs residues in birds and bird eggs reached levels higher than in any other species.

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TABLE 11

EFFECTS OF PCBs ON REPRODUCTION IN BIRDS

Ref.	Authors	Year	Species	Compound	Effects
80	Grier	1977	Bald eagles, N.W Ontario	Natural Contamination	Eggshell thinning and lowering of reprod. rate (434 ppm PCB residues in eggs).
175	Kolbye	1972	Hens	Accidental Contamination	Reduced hatchability of eggs.
176	Cecil *et al.*	1974	Hens	Aroclor 1232 & 1954 20 mg/kg	Reduction of hatchability in fertile eggs.
177	Heegele & Tucker	1974	Mallards	Aroclor 1254	Short-term eggshell thinning (single dose)
171	Risebrough & Anderson	1975	Mallards	PCBs 40 ppm & DDE 40 ppm/7 wk	Reduced egg production and hatchability. Extr. lip. residues: 344 ppm DDE, 364 ppm PCBs
165	Call & Hanell	1974	Japanese quail	Aroclor ppm 1242 312.5 & 5000* 1254 78.1 & 1250 1260 62.5* & 1000*	Significantly lower egg production and eggshell thinning in all the groups. (*Lower egg weights in marked groups.)
164	Chang & Stokstad	1975	Japanese quail	PCBs 50 ppm/15 wk	Eggshell thinning (4.5%). Increase in the percentage of cracked eggs.
178	Hill *et al.*	1976	Japanese quail 5-month old hens	Aroclor 1242 10 ppm/45 days	The shell of eggs was 4.7% (for the 1st egg) and 5.2% (for the 1st 5 eggs) thinner.
179	Cecil *et al.*	1973	Young J. quail	Aroclor 1242 100 ppm/2 months	Depression of egg production. Egg weight and eggshell thickness not affected.
166	Dustman *et al.*	1971	Chickens	Aroclor 1242 & 1254	Impaired egg production, egg hatchability and eggshell thickness.
172	Scott *et al.*	1975	White Leghorn chickens	PCBs	Some decrease in egg production. Drastic reduction in hatchability.
169	Scott	1977	White Leghorn chickens Japanese quail	PCBs 10-20-100 ppm PCBs 10-20-100 ppm	Reduction in hatchability. No effect on eggshell quality in either species.
168	Peakall *et al.*	1971	Ring doves	Aroclor 1254 10 ppm/35 days	No effect on eggshell quality.
167	Peakall *et al.*	1972	Ring doves	Aroclor 1254/ 2 generations	Low hatching of eggs in the second generation.
173	Dahlgren *et al.*	1971	Pheasants	Aroclor 1254 50 mg/wk./4 months	Lowered egg production and hatchability The hatched chicks were significantly lighter
174	Dahlgren *et al.*	1972	Penned pheasants	Aroclor 1254 12.5 & 50 mg/wk./4 m.	Egg production and hatchability were lowest in the 50 mg. group.
163	Velle	1971	Birds	PCBs & other OC	Inhibition of ovulation.



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Effects of PCBs on Reproduction in Terrestrial Mammals During Experimental or Accidental Exposure to PCBs (Table 12)

Lengthening of estrus cycle in mice[181-183] and Rhesus monkeys[184] and changes in the menstrual cycle in Yusho patients[185] were reported. Also, low mating indices in rats,[186] lower fertility in monkeys,[187] decrease in the frequency of implanted ova in mice[182,183,188] and in dogs,[189] fewer offspring per litter in rats,[190] complete failure to produce offspring in mink[191] and in dogs[189] at a certain dosage level of PCBs were reported. Fetotoxicity and abortion in rabbits,[192] embryonic mortality in mink,[193] diminished weight of whelps[188] and monkeys[187] at birth, small-for-date babies in Yusho mothers[137,194,195] stillbirths in mink,[196] dogs,[189] and man,[195] decreased survival of offspring in rats,[186] deaths of newborn kits in minks[191] and decreased percentage of whelps living more than 5 days after birth[189] have also been reported.

The effects of PCBs on reproduction vary in intensity with dosage. They occurred in a large variety of living organisms under conditions of natural exposure or laboratory experiments.

These effects were largely explained as being caused by the influence of PCBs on naturally occurring biochemical processes, by upsetting quantitatively the activity of enzymatic systems (on which they depend), in mother and fetus.

The placental transfer of PCBs was reported in marine and terrestrial mammals. In seals from the Gulf of Bothnia,[158] mice,[197,198] rats,[110] rabbits,[199,200] cows,[201] and in man (general population[202]) and in Yusho patients.[203-206]

The concentration of PCBs in rabbit fetal tissues was dose dependent.[199]

In seals, fetuses contained somewhat lower levels of PCBs and DDT than did their mothers.[158] PCB residues in rabbit fetal livers were higher than in maternal livers,[207] and the residues in the kidneys of cow fetuses were higher than in the maternal kidneys.[201]

Effect of PCBs on Development and Growth (Table 13)

Chromosomal abnormalities were observed in birds that received PCBs in their diets.[7] 100 ppm Aroclor 1254 in the diet of ring doves produced a significant increase in chromosome abnormalities. Increased aberration rates were obtained in embryos following administration of 10.0 ppm Aroclor 1254 in the diet for two generations.[167]

No evidence of mutagenic effects was observed in *Drosophila melanogaster* with Clophen A30 or Clophen A50,[209] nor in rat bone marrow and spermatogonia after single Aroclor 1242 doses of 1250, 2500 and 5000 mg/kg or repeated doses of 500 mg/kg/day, for 4 days,[210] nor in human lymphocytes after treatment in media containing 100.0 ppm Aroclor 1254 for 24 hours and the last 8 hours of a 52-hour experiment.[211]

Teratogenic effects were reported in birds experimentally exposed to PCBs.[7] Beak abnormalities in chicks were obtained after injection of Aroclor 1242 into the yolk sac.[212]

Teratogenic effects in offspring were produced also by feeding PCBs to hens.[176]

Among terns from Great Gull Island, NY., naturally exposed to PCBs, having a muscle PCB residue level of 5.0–175.0 ppm[63] and 25.0 ppm,[64] a high number of deformities of the eye, bill, and leg plus loss of flight feathers and failure to hatch were observed.[63,64,213]

No teratogenic effects were obtained in rats given Aroclor 1242, 10 or 30 mg/kg[188] or in rabbits given 10, 50 or 100 mg Aroclor 1254 per kg.[192]

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TABLE 12

EFFECT OF PCBs ON REPRODUCTION IN TERRESTRIAL MAMMALS

Ref.	Authors	Year	Species	Compound, dosage	Effects
181	Johansson *et al*	1972	NMRI mice	PCBs 20 mg/kg (1 inj.)	Lengthening of the estrus cycle by one d. / 3 cycles
182	Kihlström *et al*	1973	NMRI mice	Clophen A60 25 μg/62 d. to the nursing mothers.	Increase in the length of the estrus cycle. Decrease in the frequency of implanted ova/offspring
183	Orberg & Kihlström	1973	NMRI mice	Clophen A60 25 μg/d. Chronic exposure	Lengthening of estrus cycle. Decrease in the frequency of implanted ova.
188	Kihlström *et al.*	1975	NMRI mice	PCBs 50 mg/kg/wk/4 wk beginning the day of deliv	The frequency of implantation in the young decreased from 94% (controls) to 75%.
186	Keplinger *et al*	1971	Rats	Aroclor 1242 & 1254 100 ppm in diet	Low mating indices. Decreased survival in pups.
				Aroclor 1260 100 ppm in diet	No effect.
190	Linder *et al*	1974	Rats	Aroclor 1254 20 & 100 ppm in diet	Fewer offspring per litter
				Aroclor 1260 20 & 100 ppm in diet	No effect.
208	Jonsson *et al*	1976	PCBs		High doses markedly reduced reproduction
192	Villeneuve *et al*	1971	Rabbits (pregn.)	Aroclor 1254 12.5 mg/kg/d. first 28 d.	Abortions. Fetotoxicity
193	Aulerich *et al*	1971	Mink	Coho salmons and other Great Lake fishes	Embryonic mortality. Death of newborn kits
191	Ringer *et al*	1972	Mink	Aroclor 1254 5, 10 ppm	Complete failure to produce offspring
196	Aulerich *et al*	1973	Mink	Coho salmons of Lake Michigan	58% of whelped 55% of the young were stillborn. Toxicity varied inversely with chlorine content
189	Jensen *et al*	1977	Dogs	PCBs 22, 11 mg/d. doses	Decrease in the number of whelps per bitch
				PCBs 3.3 ppm + DDT 3.3 ppm.	The number of delivering bitches, whelps per bitch, whelps living after 5 days and weight of whelps was decreased. The number of stillborns was increased.
				PCBs 11 mg/d/66 d. (beginning 1 m. before mating)	No whelp was born in this group
187	Allen	1975	Monkeys	Aroclor 1248 2.5 ppm in diet	Lower fertility. Diminished weight of young at birth.
195	Nishimura	1973	Man	Yusho patients	Stillbirths.

TABLE 13

EFFECTS OF PCBs ON DEVELOPMENT AND GROWTH

Ref.	Authors	Year	Species	Compound, dosage	Effect
209	Nilsson & Ramel	1974	*Drosophila melanogaster*	Clophen A30 Clophen A50	No chromosomal damage was observed
7	Anonymous	1972	Birds	PCBs in diet	Some evidence of chromosomal damage
167	Peakall *et al*	1972	Ring doves	Aroclor 1254 100 ppm	Significant increase in chromosomal abnormalities in embryos
				10 ppm/2 generations	13/17 embryos had aberration rates exceeding the mean control rate and 4/17 exceeding the highest control rate. One chromosomal rearrangement was observed
210	Green *et al*	1975	Rats	Aroclor 1242 1250, 250 or 5000 mg per kg in single dose	No evidence of mutagenic effects in bone marrow and spermatogonia.
				500 mg/kg/d/4 d	Idem.
211	Lee Spingarner *et al.*	1972	Man	Aroclor 1254 100 ppm/24 hr + last 8 hr of 52 hr	No effect on chromosomes of lymphocytes exposed "in vitro" was observed in a 52 hours experiment.
212	Mc Laughlin *et al.*	1963	Chick eggs	Aroclor 1242 inj. into the yolk sac.	Beak abnormalities in young
7	Anonymous	1972	Birds	PCBs in diet	Some evidence of teratogenesis
176	Cecil *et al.*	1974	Hens	Aroclor 1232 and 1254 20 mg/kg	Teratogenic effects.
61	Anonymous	1972	Terns of Long Island Sound	Natural exposure	A high incidence of deformities. Muscle PCB residues range was 5.0–175.0 ppm
64	Hays & Risebrough	1972	Common and roseate terns of Great Gull Island, NY ('69–'70)	Natural exposure	Eye, bill and foot deformities, flight feathers loss and failure of hatch. Muscle PCB residues in young terns, 25 ppm
213	Hays & Risebrough	1972	Terns from Great Gull Island, NY	Natural exposure	Bill and leg deformities and missing flight feathers
187	Allen	1975	Monkeys	PCBs	Pregnancies produced small infants
137	Yamaguchi *et al.*	1971	Man	Yusho mothers	Small babies

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TABLE 13 (*continued*)

EFFECTS OF PCBs ON DEVELOPMENT AND GROWTH

Ref	Authors	Year	Species	Compound, dosage	Effect
194	Funatsu	1972	Man	Yusho mothers	Small babies
195	Nishimura	1973	Man	Yusho mothers	Substandard body weight in new born
214	Fraumeni	1974	Man	Yusho babies	Growth retardation, early teeth eruption
215	Kuratsune *et al.*	1971	Man	Yusho children	Diminished growth, in boys
216	Yoshimura	1971	Man	Yusho children	Diminished growth, in boys

TABLE 14

EFFECTS OF PCBs ON LIVER MORPHOLOGY

Ref	Authors	Year,	Species	Compound, dosage	Effects
223	Ito *et al.*	1973	Mice	Kanechlor-500, 100 & 250 ppm Kanechlor-400 & -300 300, 400 & 500 ppm	Amyloid degeneration
217	Treon *et al.*	1956	Rats	Aroclor 1242 & 1254, vapors	Liver enlargement
218	Grant *et al.*	1971	Rats	Aroclor 1254, 500 mg/kg/1d.	Significantly enlarged livers. Increased liver lipids.
219	Keplinger *et al.*	1971	Rats	Aroclor 1242 & 1254 100 mg/kg	Increased liver weight.
220	Kimbrough *et al.*	1972	Rats	Aroclor 1260	Increase in fat droplets and smooth endoplasmic reticulum (SER). SER cisternae were condensed in hyaline inclusions.
221	Northach & Allen	1972	Rats	Aroclor 5660, 10 ppm. Aroclor 1260 0.2 ppm/21d.	Hypertrophy of the liver. Proliferation of SER and multilayered concentric membrane arrays
222	Vos & Nottenboom-Rom	1972	Rabbits	Hexachlorobiphenyl	Lipid accumulation, pigment deposits, nuclear changes and necrosis of liver parenchymatous cells
224	Rogers *et al.*	1976	Rat liver lysosomes *in vitro*	Aroclor 1254	Labilization of lysosomal membranes and consequent release of hydrolytic enzymes into the cytoplasm, cellular damage
228	Nishihara & Yamamoto	1972	Guinea pigs (M)	Kanechlor-400 100 mg/kg single dose	Proliferation of SER which persisted 2 months
			Rats	Kanechlor-400 100 mg/kg single dose + cycloheximide	Slight inhibition of SER proliferation
				Kanechlor-400 200 mg/kg	The glycogen deposits disappeared completely
225	Iatropoulos *et al.*	1977	Rhesus monkeys (F)	Clophen A30 2,5,4'-trichlorobiphenyl	Dose dependent degenerative changes in the liver Reversible changes in the endothelial cells of small vessels with secondary hypoxia and degenerative changes in the liver, the kidney and central nervous system.
			Lactating Rhesus monkeys (F)	Clophen A30	Slight to moderate degenerative changes in infant monkeys. The severity of these changes increased with age.
227	Hirayama *et al.*	1969	Man	Yusho patients	Increase in SER (liver biopsy)

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Monkeys fed diets containing Aroclor 1248 produced small infants.[167]

Substandard body weight in new born Yusho babies,[137,196,197] growth retardation and early teeth eruption[214] and diminished growth in boys[215,216] were reported after the PCBs poisoning in Japan.

Effects of PCBs on Liver Morphology (Table 14)

In animal experiments, exposure to PCBs brought about the following: significantly enlarged livers,[217-219] lipid accumulation (increased number of lipid droplets), proliferation of the smooth endoplasmic reticulum (SER) in the cytoplasm of centrilobular parenchymatous cells,[220-222] adenomas, carcinomas, adenofibrosis (proliferation of bile ducts within a connective tissue rich in collagen fibers—(see Table 25), amyloid degeneration[223] and degenerative changes, and necrosis due either to labilization of lysosomal membranes and consequent release of hydrolytic enzymes into the cytoplasmic matrix[224] or to reversible changes in the endothelial cells of small vessels, with secondary hypoxia.[225]

The morphologic changes were more pronounced in females than in males.[226] The size and quality of the morphologic changes were correlated to the dosage.[226]

Increase in SER was reported in a Yusho patient (liver biopsy) in 1969.[227]

The proliferation of SER, of the tubulo-vesicular type, as being the morphologic expression of increased enzymatic activity was considered an adaptive phenomenon, used by the cell as a resource (of defense) to get rid of xenobiotics.

The endoplasmic reticulum may also proliferate in the form of smooth cisternae, arranged in whorls, which may be very large or multiple and occupy most of the available cytoplasmic space.

An increased phospholipid to protein ratio and a decreased ratio of cholesterol to proteins in the concentric membrane arrays within the liver cells of chlorinated-aromatic-hydrocarbon-treated rats, suggested to Norbach and Allen,[223] that these structures are a distinct entity of the endoplasmic reticulum which is more suited to appropriating foreign hydrophobic compounds to the enzymes of the membranes. In accord with this concept, the smooth cisternae whorls may also be seen as an adaptive response of the liver cell to the exposure to increased amounts of xenobiotics.

These morphologic changes in the SER may be also the morphologic substrate for the induction of enzymatic systems that upset normal metabolic pathways in the cell and so explain most of the biologic effects of xenobiotics.

Effects of PCBs on Enzymatic Activity (Tables 15 and 16)

PCBs were shown to induce the activity of a number of enzymes and to inhibit the activity of others.

Highly chlorinated PCB mixtures were more potent inducers of enzymatic activity.[162,229-232] Aroclor 1254 is a more potent inducer than Aroclor 1242[229] and than 1216.[233] Pentachlorobiphenyl was however more effective than hexachlorobiphenyl as an enzyme inducer in the rat,[230] and Aroclors 1242 through 1254 (in the intermediary range of chlorination) were more effective inhibitors than Aroclors 1221 and 1268 of oligomycin-insensitive Mg^{2+} ATPase, in fish.[234] On the other hand, it seems that the degree of chlorination is of minor significance for the depression of NADH cytochrome c reductase and succinate cytochrome c reductase in the beef heart heavy microsomal fraction.[235]

N-demethylase is more sensitive to the activating effect of Aroclor 1260 than to that of Aroclor 1254, while *O*-demethylase is more sensitive to the activating effect of

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TABLE 15

EFFECTS OF PCBs ON ENZYMATIC ACTIVITY IN FISH AND BIRDS

Ref.	Author	Year	Species	Compound, dosage	Tissue	Effects
242	Cutkomp *et al.*	1972	Blue-gill fish	PCBs	Muscle	Inhibition of oligomycin-insensitive Mg^{2+}-ATPase (*in vitro*) Less effective in liver, kidney, and brain
234	Desaiah *et al.*	1972	Fish	PCBs	4 tissues	Inhibition of oligomycin-insensitive Mg^{2+}-ATPase
				Aroclor 1242	Brain	Inhibition of $(Na^+ + K^+)$-ATPases.
24	Davis *et al.*	1972	Rainbow trout	Aroclor 1242 & 1254 400 ppm	Gill	Inhibition of ATPases.
244	Risebrough *et al.*	1968	Pigeons	PCBs	Liver	Activation of microsomal hydroxylating enzymes
245	Lincer & Peakall	1970	American kestrels	PCBs	Liver	Activation of microsomal hydroxylating enzymes
163	Velle	1971	Birds	PCBs	Liver	Increased steroid hydroxylase activity
229	Bailey & Bunyan	1972	Pigeons & quails	Aroclor 1254	Liver	Increase in microsomal proteins. Induction of cytochrome P-450 activity. Aroclor 1254 is a more potent inducer.
				Aroclor 1242		
241	Bitman *et al.*	1972	Japanese quail	PCBs & PCTs		Initial inhibition followed by stimulation of pentobarbital metabolism.
242	Cutcomp *et al.*	1972	Fat head minnows	Aroclor 1242/4m	Brain	75% inhibition on mitochondrial Mg^{2+}-ATPase and 35% in $(Na^+ + K^+)$ ATPase
246	Koch *et al.*	1972	Fat head minnows (reared in aquaria)	Aroclor 1242 — Aroclor 1254/4m		Inhibition of mitochondrial Mg^{2+}-ATPase in brain in brain.
247	Goldstein *et al.*	1975	Chickens	Hexachlorobiphenyl 400 ppm/3 wk		Increase of *p*-nitrophenol glucuronyl transferase, *d*-aminolevulinic acid synthetase and cytochrome P-450 activity.
248	Dieter	1974	Coturnix quail	Aroclor 1254/12 wk		Increased activity of plasma enzymes.
249	Dieter	1974	Coturnix quail	Aroclor 1254		Inhibition of biochemical adaptation to motion stress. The enzyme responses to stress were 2-3 times greater.
250	Dieter	1975	Wild starlings	PCB 5-100 ppm/ 12 wk		Induction of lactate dehydrogenase and creatinine kinase activity.
169	Scott	1977	White Leghorn Chickens	PCBs	Plasma	Decreased glutathione peroxidase activity.
					Liver	Induction of microsomal benzpyrene hydroxylase.

TABLE 16

EFFECTS OF PCBs ON ENZYMATIC PRODUCTION IN MAMMALS

Ref.	Authors	Year	Species	Compound, dosage	Effects in Liver
238	Kimmel & Clausen	1973	Mice	Aroclor 1254 1500 ppm/7 d.	Induction in cytochrome P-450 and mixed function oxidase activities.
251	Abraham	1974	Charles River CD-1 mice	PCBs 500 ppm/7 d	Increased demethylase activity. Decreased glucose-6-phosphatase activity.
230	Fujita *et al.*	1971	Rats	Di- tetra -penta -hexachloro biphenyls	2,4,5,3',4'-pentachlorobiphenyl was the most potent inducer.
252	Benthe *et al.*	1972	Rats	Di- and tetra-chlorobiphenyls (CB)	Stimulation of microsomal drug oxidizing enzymes is effective with tetra-CB
233	Bickers *et al.*	1972	Rats	Aroclor 1254 25 mg/kg/6 d.	Two fold increase in aniline hydroxylase, ethyl morphine *N*-demethylase and cytochrome P-450 and b_5 activity. Increased microsomal proteins
				Aroclor 1216	1.4 fold increase in ethyl morphine *N*-demethylase and and cytochrome P-450 activity.
253	Letterst & Van Loon	1972	Rats	PCBs 150 ppm/kg/30d	Induction of nitroreductase and nitrohydroxylase activity. More active than DDT.
236	Letterst *et al.*	1972	Rats	Aroclors 1240–1260	Induction of demethylase, nitroreductase and cytochrome P-450 activity. Decreased activity of glucose-6-phosphatase. Aroclor 1260 is the more effective inducer.
221	Norbech & Allen	1972	Rats	Aroclor 1254, 200 ppb	Increased microsomal proteins/g of liver.
				Aroclor 5460 1 ppm	Increased esterase activity.
239	Bickers *et al.*	1973	Rats	PCBs skin application 25 mg/kg/d.6 d.	Induction of cytochrome P-450, ethylmorphine *N* demethylase, aniline hydroxylase and benzpyrene hydroxylase. More than DDT.
162	Chen & DuBois	1973	Rats	PCBs	Increased activity of *N*-demethylase, most sensitive to Arochlor 1260, and of *O*-demethylase, most sensitive to Arochlor 1254.

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240	Bickers *et al.*	1974	Rats	PCBs	3-fold induction of cytochrome P-448 and 10-fold induction of Benzo (a)-pyrene hydroxylase activity. More potent inducers than DDT.
254	Den Tonkelaar & Van Esch	1974	Rats	PCBs 2–200 ppm/2 wk	Increased aniline hydroxylase, aminopyrine demethylase and hexobarbital activity.
218	Grant *et al.*	1974	Rats	Aroclor 1254 20 mg/kg/246d 2 mg/kg	Increase in microsomal enzyme activity. No effect.
231	Johnstone *et al.*	1974	Rats	Pure PCB compounds	Increase in *N*-demethylase, *O*-demethylase, aniline hydroxylase and nitroreductase activity.
255	Alvares & Kappas	1975	Rats (pregnant)	PCBs	Induction of aryl hydrocarbon hydroxylase in fetus, placenta and in neonatal livers, during lactation.
256	Cappon & Nicholls	1975	Rats	Aroclor 1254 i.p. 200 mg/kg/2 d	Increased incorporation of ^{14}C-phenylalanine-tRNA into polypeptide.
257	Fulfs & Abrahamson	1976	Rats	Aroclor 1221 25 mg/kg/7 m	Inhibition of glucose 6-phosphatase activity.
237	Morniami *et al.*	1976	Rats	PCBs Single oral dose of 100 mg/kg	Induction of cytochrome P-450, NADPH cytochrome c reductase, *p*-nitroanisole *O*-demethylase, benzpyrene hydroxylase, glutathione S-transferase and UDP-glucuronoyl transferase activities.
200	Villeneuve *et al.*	1971	Rabbits (pregnant)	Aroclor 1254 10 mg/kg/28 d below 10 mg/kg	Induction of aniline hydroxylase and aminopyrine *N*-demetylase activities. No-effect level.
258	Sharp *et al.*	1974	Rabbits (kidney) Beef (brain)	PCBs	Inhibition of $(Na^+ + K^+)$ ATPase activity. Inhibition of $(Na^+ + K^+)$ ATPase activity.
235	Pardini	1971	Beef (heart)	PCBs	Inhibition of NADH-cytochrome c reductase and succinate cytochrome c reductase activities by 80%.
259	Wilson & Sharp	1972	Beef (brain)	Aroclor 1251 Aroclor 1254	Inhibition $(Na^+ + K^+)$ ATPase activity by 50%.
189	Jensen *et al.*	1977	Dogs	PCBs 3.3 & 11.0 ppm in diet	Increased concentrations of liver cytochrome P-450 and renal cadmium.



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Aroclor 1254.[102] That is, one PCB mixture may be a more potent inducer for one enzyme and a poorer inducer for another within a given animal species.

A relatively low concentration of PCBs is enough to activate some enzymes, while for other enzymes the concentration of PCBs has to be very high and/or the PCBs mixture used has to be highly chlorinated. Aroclors 1240 through 1260, at a dosage of 0.5 mg/kg for four weeks increase the activity of nitroreductase, but only a dosage of 50 mg will induce cytochrome P450, in rats.[236]

The degree of induction of enzymatic activity may differ in the organs of the same animal. The inhibitory effect of PCBs on the activity of oligomycin-insensitive Mg^{++} ATPase (present in endoplasmic reticulum) is more effective in muscle homogenates as compared to kidney, brain, and liver in Blue gill fish.[236]

The peak activity of several enzymes occurred between 2 weeks and 2 months in rats, after a single oral dose of 100 mg PCBs per kg.[237]

The induction of *N*-demethylase in rats was more pronounced in males than in females, and more in young than in adults.[167]

Organochlorine compounds have in common the biologic effect of upsetting the homeostasis of enzymatic activity. Generally, PCBs seem to be more potent inducers of enzymatic activities than DDT[238] and the effect is more persistent.[239] PCBs are more potent inducers of the hepatic mixed function oxydase system than DDT in rats[240] and mice.[239] Aroclor 1254 caused a 360% induction of cytochrome P450 activity, but lindane and DDT only induced 93% and 76%, respectively.[240] Aroclor 1260 has an estradiol-degrading potential four to five times that of *p,p'*-DDE or technical grade DDT.[31] After a single skin application of PCBs to rats, the enzyme induction was greater and persisted longer than with DDT.[239] However, PCBs were less effective than DDT in their inhibitory effect on mitochondrial Mg^{++} ATPase, in fish muscle homogenate.[236]

Stimulation of the enzymatic activity of pentobarbital metabolism by PCBs in the Japanese quail, follows an initial inhibition that did not occur with DDT and its analogues.[241]

Differences in the effects on enzymatic systems may explain differences in the biologic effects of organochlorine compounds.

Effects of PCBs on Drug Metabolism (Table 17)

PCBs were shown to reduce the sleeping time induced by several hypnotic drugs like phenobarbital, pentobarbital, and hexobarbital, the time of zoxazolamine-generated paralysis, and the time of action of other drugs. The reduction of drug-induced sleeping time was proportional to the chlorine content of the PCBs mixture used[232] and to the dose of PCBs,[208] and it was inversely proportional to the time elapsed between the administration of the PCBs and the performance of the test.[261] Divided doses were less active than a comparable total single dose.[131]

The reduction of phenobarbital sleeping time was greater in male quails than in females.[232] The reduction of hexobarbital sleeping time was equal for male, female, castrated, and sex-hormone-treated rats.[158] The effect of PCBs + DDT on the hexobarbital sleeping time was greater than that obtained with a 2.5 times higher dosage of PCBs when administered alone, and the effect of PCBs + β-BHC was that obtained with a ten times higher dosage of PCBs when given alone. The doses of DDT and β-BHC were respectively about twice and eight times lower than those which would have given the same effect when given alone.[264]

The paralysis following administration of zoxazolamine to rats, which had previously received Aroclor 1216, was reduced by about 50% and in rats which

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TABLE 17

EFFECTS OF PCBs ON DRUG METABOLISM

Ref.	Authors	Year	Species	Compound	Effects
232	Cecil *et al*	1975	Japanese quail	Aroclor 1221 through 5460 Single dose of 100 mg/kg	Prolonged phenobarbital sleeping time after 2 hours, similar to controls after 24 hours and reduced by 50% after 48 hours. The reduction was greater in males and was correlated with the percentage of chlorine in the PCBs. The effect was lower with PCTs.
260	Arachi & Tanaka	1974	Mice (F)	PCBs	Reduction of hexobarbital sleeping time, parallel to the dose of PCBs.
261	Arachi & Tanaka	1974	Mice (F)	PCBs 20 mg/kg, DDT 200 mg/kg and β-BHC 100 mg/kg. PCBs 20 mg/kg + DDT 200 mg/kg PCBs 5 mg/kg + β-BHC 25 mg/kg	Reduction of hexobarbital sleeping time (minimum effective doses). Reduced to 44% after 2 days. 63% ↑ 7 ↑ 89% ↓ 14 ↓ as controls 21 65% ↑ 2 ↑ 70% ↓ 7 ↓ 92% after 14 days.
263	Kimura & Taniguchi	1975	Mice	PCBs	Shortened hypnotic effect of hexobarbital sodium.
			Rats	PCBs	Shortened hypnotic effect of hexobarbital sodium.
264	Street *et al.*	1969	Rats (F)	Aroclor 1221 50 mg/kg Aroclor 1248 50 mg/kg Aroclor 1268 50 mg/kg	Reduction of hexobarbital sleeping time by 11%. Reduction of hexobarbital sleeping time by 35%. Reduction of hexobarbital sleeping time by 48%.

TABLE 17 (*continued*)

EFFECTS OF PCBs ON DRUG METABOLISM

Ref.	Authors	Year	Species	Compound	Effects
233	Bickers *et al.*	1972	Rats	Aroclor 1254 25 mg/kg/6 d	Abolishment of zoxazolamine paralysis
				Aroclor 1216 mg/kg/6 d	Reduction of zoxazolamine paralysis by about 50%
				Aroclor 1254 25 mg/kg/6 d	Reduction of hexobarbital sleeping time by about 75%
				Aroclor 1216 25 mg/kg/6d	by about 50%
131	Tanaka & Komatsu	1972	Rats	Kanechlor-500 2 mg/kg/d/3d	to 49%
				Kanechlor-0.4 mg/kg/d/15d	to 108%
				30d	to 82%
				/45d	to 87%
				/53d	to 88%
					of hexobarbital sleeping time
				Kanechlor-400 100 mg/kg/3d	Reduction equal for female, male, castrated and sex hormones treated rats.
192	Villeneuve *et al.*	1972	Rats	Aroclor 1254 chronic exp.	Reduction of pentabarbital sleeping time
				Aroclor 1260 chronic exp.	Reduction of pentabarbital sleeping time
				Aroclor 1221 chronic exp.	No effect.
231	Johnstone *et al.*	1974	Rats	PCBs	Reduction of phenobarbital sleeping time.

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received Aroclor 1254, was abolished.[253] PCBs were the most potent inducers of zoxazolamine-metabolizing enzymes.[262]

There are quantitative and qualitative differences between xenobiotics so far as their influence on enzymatic activity is concerned. The resultant of the action of the xenobiotics of the internal milieu added to the biochemical individuality of drug-metabolizing enzymes will decide the plasma level of drugs and in turn their efficacy.

Effects of PCBs on Lipid Metabolism (Table 18)

Increase in plasma cholesterol in rats given 1000 and 2000 ppm PCBs in the diet[263] and 0.5, 2.5, 5.0, and 50.0 mg Kanechlor-400 per day during 2–6 weeks[266] and PCTs[267] were reported. A higher dose of Kanechlor-400, 50 mg per day for 2–6 weeks, was necessary in order to obtain an increase in plasma triglycerides in rats, whereas the plasma cholesterol and phospholipids increased with only 0.5 mg Kanechlor-400 under the same conditions.[266] A tenfold increase in serum triglyceride level was produced in rats given 100 mg Kanechlor-400 per kg during 4 weeks.[266] In rabbits given 8 ccs PCBs 1% in olive oil per day for 3 days, a twofold increase of total liver lipids and triglyceride levels was noted. When the treatment was extended to 11 days, an abnormal increase in serum triglyceride levels occurred.[269] In *Macaca mulatta* monkeys given 100 or 300 ppm Aroclor 1248 in the diet for 2–3 months, total serum lipids, cholesterol and triglycerides were reduced.[193] In Yusho patients increased serum triglyceride levels were reported.[126,270–272]

Effects of PCBs on Liver Porphyrins (Table 19)

PCBs produced hepatic porphyria in mice,[276] in rats, rabbits, quail, and chickens.[275] The increase in liver porphyrins was proportional to the dosage. Female rats[276] and female Japanese quail[277] were more susceptible than males to hepatic porphyria. Porphyrin granules were associated with lysosomes in the centri-lobular hepatocytes near the bile canaliculi, in mice and rats given Aroclor 1254, 25 ppm in diet[274] or Aroclor 1221, 25 ppm.[257] A 20-fold increase in the activity of mitochondrial ALA-synthetase occurred in male Japanese quail given 500 ppm Aroclor 1260 during 7 days and in female Japanese quail given only 100 ppm. The no-effect level was considered to be 0.1 ppm.[277]

Marked increase in the urinary excretion of coproporphyrin and fecal excretion of protoporphyrin was observed: in rats that received 500 ppm Kanechlor-300 or Kanechlor-500 in the diet,[278] in rabbits following 27 dermal applications of 118 mg PCBs for 38 days[279] or subcutaneous injections of Kanechlor-400 for 55 days[280] and in chickens given Phenchlor PD60, Clophen A60 or Aroclor 1260, 400 ppm.[281] PCBs were claimed to be nonporphyrinogenic in the guinea pig.[282]

A rapid accumulation of uroporphyrin III occurred in liver cell culture of chicken embryos treated with PCBs—by inhibition of uroporphyrinogen decarboxylase.[283]

The porphyrinogenic effect of PCBs was attributed to compounds that were detected in very small quantities in the technical PCBs. Pure tetrachlorobiphenyl did not produce porphyria in rats,[284] whereas some chickens from a group given hexachlorobiphenyl became porphyric.[6,7] These two experiments may suggest that higher chlorinated biphenyl compounds are responsible for the porphyrinogenic action or the tetrachlorobiphenyl was ineffective because of an inadequate dosage.

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TABLE 18

EFFECTS OF PCBs ON LIPID METABOLISM

Ref.	Authors	Year	Species	Compound, dosage	Effects
265	Kiriyama *et al.*	1972	Rats	PCBs in the diet 1000 and 2000 ppm	Increase in plasma cholesterol (no effect if konjac mannan – a nonnutritive polysaccharide was administered simultaneously).
267	Kiriyama *et al.*	1974	Rats	PCBs	Significant increase in plasma and liver cholesterol.
				PCTs	Increase in plasma cholesterol.
				PCB substitutes	No effect, with the exception of kanetherm-T.
266	Nagai *et al.*	1971	Rats	Kanechlor-400 0.5, 2.5, 5, 50 mg/d/2 6 wk	Increase in plasma triglyceride in the 50 mg group. Plasma cholesterol and phospholipids increased in all the groups with the dosage.
268	Tanaka *et al.*	1969	Rats	Kanechlor-400 100 mg/kg 4 wk	Tenfold increase of serum triglyceride level.
236	Letterst *et al.*	1972	Rats	Aroclor 1242 1260 0.5, 5, 50, 500 mg/kg/4 wk	Increase in liver triglyceride level. The greatest increase was obtained with Arochlor 1248.
273	Nagai *et al.*	1972	Rats	Kanechlor-400 1 mg/kg/d/30 d	The rate of incorporation of ^{14}C-acetate into skin fatty acids of sterol esters was enhanced, suggesting that the chain elongation and desaturation of those fatty acids were activated.
269	Ito *et al.*	1971	Rabbits	PCBs 1% in olive oil 8 cc/d/3 d	Twofold increase of liver total lipid and triglyceride levels.
				11 d	Abnormal increase in serum triglyceride levels.
187	Allen	1975	Monkeys	Aroclor 1248 100 and 300 ppm/1 m.	Reduced total serum lipids, cholesterol and phospholipids.
270	Uzawa *et al.*	1969,	Man	Yusho patients	Serum triglyceride levels higher than 300 mg/100 ml in 60 out of 396 patients.
271		1971			
272	Uzawa *et al.*	1972	Man	Yusho patients	Increase in serum triglyceride levels: 136 mg/100 ml (up to four times the normal values).
126	Okumura *et al.*	1974	Man	Yusho patients	Increase of plasma triglycerides: 134 mg/100 ml.

TABLE 19

EFFECT OF PCBs ON LIVER PORPHYRINS

Ref.	Authors	Year	Species	Compound, dosage	Effects
274	Fulfs	1976	Mice	Aroclor 1254 20 mg/kg	*Porphyrin granules* associated with lysosomes in centrilobular hepatocytes.
			Rats		
270	Kimbrough *et al*	1972	Mice	PCBs	Hepatic porphyria.
			Rats		
285	Goldstein *et al.*	1973	Mice	Aroclor 1254	Hepatic porphyria.
		1973	Rats	10 mg/kg/d/4 m	
278	Kawanishi *et al.*		Mice	Kanechlor-300 500 ppm	Marked increase in urinary excretion of copro-porphyrin and fecal excretion of protopor-phyrin.
			Rats	Kanechlor-500 500 ppm	
276	Goldstein *et al.*	1974	Mice	Aroclor 1254 100 ppm	Increased liver porphyrins (correlated to dose)
			Rats	Aroclor 1242 10, 100 ppm/21 d	Increased liver porphyrins (correlated to dose) Female rats more sensitive.
284	Kawanishi *et al.*	1974	Mice	Tetrachlorobiphenyl (pure)	It did not produce porphyria.
			Rats		
257	Fulfs & Abraham	1976	Mice	Aroclor 1221 25 ppm/7 m	*Porphyrin granules* in the centrilobular hepato-cytes, near the bile canaliculi (first noted at 6 months).
			Rats		
282	Vos & Van Driel-Grootenhuis	1972	Guinea pigs	PCBs	Nonporphyrinogenic.
279	Vos & Beems	1971	Rabbits	PCBs dermal application	Increased excretion of copro- and protoporphyrins.
280	Miura *et al.*	1973	Rabbits	Kanechlor-400 s.c. inj. 55d	Porphyrinogenic.
275	Vos	1972	Rabbits	PCBs	Hepatic porphyria
			Rats		
			Quail		
			Chickens		
247	Goldstein *et al*	1974	Chickens	Hexachlorobiphenyl in diet 400 ppm/3 w.	Some chickens become porphyric.
281	Vos & Koeman	1970	Chickens	Phenchlor PD60, Clophen A60, Aroclor 1260, 400 ppm	Increased excretion of copro- and protoporphyrins.
283	Sinclair & Granick	1974	Chick embryos	PCBs	Rapid accumulation of uroporphyrin III in liver cells in culture. (Inhibition of uroporphyrinogen decarboxylase)

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TABLE 19 (*continued*)

EFFECT OF PCBs ON LIVER PORPHYRINS

Ref.	Authors	Year	Species	Compound, dosage	Effects
277	Vos *et al*	1971	Japanese quails (males)	Aroclor 1260 50–1000 mg/kg 7 d	Porphyrin fluorescence: 20-fold increase in mitochondrial ALA-synthetase at 5000 mg/kg level 10-fold increase at the 50 mg/kg level. The no-effect level was 0.1 mg/kg (liver residue 10.5 ppm.)
			(females)		20-fold increase of ALA-synthetase activity in the 100 mg/kg group.

TABLE 20

OTHER METABOLIC EFFECTS OF PCBs

Ref.	Authors	Year	Species	Compound, dosage	Effects
241	Bitman *et al.*	1972	Rats (M) & (F)	Aroclor 1242	Decrease of about 50% of the liver vitamin A
			Japanese quail (M) and females kept in the dark	Aroclor 1242	Decrease of about 50% of the liver vitamin A
179	Cecil *et al.*	1973	White Leghorn chickens	PCBs in diet	Potentiation of a vitamin E-selenium deficiency
289	Greichus *et al.*	1975	Penned white pelicans	100 mg PCBs/d/10 d.	Significant lowering of potassium, calcium and protein serum levels.
160	Scott	1977	Young Japanese quail	Aroclor 1242 100 ppm 2 m	Increase in liver weight Decrease in liver vitamin A level by about 50%
286	Bastomsky *et al.*	1975	Rats	PCBs	Decrease in serum bilirubin level by almost 50%
			Rats	Aroclor 1254 25 mg/kg d/4 d/in corn oil	Hyperbilirubinemia—no effective increase in UDP-glucuronosyntransferase (1.4.1.7.). Serum bilirubin levels were significantly decreased
			Gunn rats		
287	Hirayama *et al.*	1974	Man	Yusho patients	Significant decrease of serum bilirubin. The levels were negatively correlated with PCBs and triglyceride blood levels.



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Other Metabolic Effects of PCBS (Table 20)

Besides these metabolic actions of PCBs, several others were reported:

A decrease of nearly 50% in serum bilirubin was described in Gunn rats, genetically deficient in UDP glucuronosyltransferase (2.4.1.7), given 25 mg Aroclor 1254 per kg per day for 4 days in corn oil.[296] In Yusho patients, a significant decrease was noted in serum bilirubin, negatively correlated with PCB and triglyceride blood levels.[297]

A decrease of about 50% was found in the liver vitamin A in rats and Japanese quail given Aroclor 1242 for 2 months.[179,298] A potentiation of a vitamin E-selenium deficiency was reported in white Leghorn chickens given PCBs in the diet.[299]

A significant lowering of serum potassium, calcium and of serum proteins was observed in penned white pelicans that received 100 mg of PCBs per day for 10 days.[299]

Hormonal Effects of PCBs (Table 21)

Increases in the metabolism of gonadal steroid hormones in pigeons[266] of testosterone, estradiol 17 β and 4-androstene-3, 17 dione in one-week-old white Leghorn cockerels,[298] of estradiol in the American kestrel,[265] of estrogen in ring doves,[170] of progesterone in rats,[300] of estrogens and dehydroepiandrosterone in the adult boar,[301] and of androsterone, etiocolanolone and dehydroepiandrosterone in Yusho patients[302] were reported. Inhibition of 17 β [^{3}H] estradiol binding, to the uterine receptor, by PCBs given to rats[303] and pathologic changes in the uterine horns (stenosis and occlusions) in seals with high PCBs and DDT residue levels were also described. An estrogenic activity of PCBs and PCTs, evaluated by the 18-hour glycogen response of the immature rat uterus test, was shown.[201,203]

One of the consequences of the low sexual hormones levels was a decrease in primary and secondary sexual characteristics. A decrease in comb and wattles and of the testicular weight in white Leghorn cockerels,[296-297] and a decrease of seminal vesicles in mice[298] occurred following PCBs administration. Another consequence of the changes induced by PCBs, in the metabolism of gonadal steroid hormones and other hormones like those of the thyroid and adrenal glands, was an impairement of the reproduction success at several stages of this process.

The effects of PCBs on the thyroid hormones were studied experimentally in animals. A decreased PBI serum level was found in rats given PCBs.[299,300] A reduced binding of thyroid hormones to serum proteins was reported, as shown by enhanced resin uptake of ^{125}I-triiodothyronine from serum. Also, an increased biliary excretion of ^{125}I-thyroxine and a larger proportion of biliary ^{125}I present as thyroxine-glucuronide were reported. In support of an increased degradation of thyroid hormones rather than a secretion failure by the thyroid gland, as the cause of the lowered thyroid hormones serum levels, is the reduced binding of thyroid hormones to proteins (that is, a higher percentage of free hormones allowed for their more active degradation in the liver).[299,300] Further, the negative feed back of the adenohypophysis-thyroid axis has been demonstrated by the following findings: enlarged thyroid glands in bobwhite quail,[304] enhanced uptake by the thyroid gland of ^{131}I in rats,[300] and ultrastructural features of hyperfunction in the thyroid cells that secrete thyroxine and triiodothyronine.[299]

The decreased levels of circulating gonadal and thyroid hormones seem therefore to be the result of their increased degradation by liver enzymes activated by the presence of PCBs in the animal body.

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TABLE 21

HORMONAL EFFECTS OF PCBs IN BIRDS AND MAMMALS

Ref.	Authors	Year	Species	Compound	Effects on the Gonads
244	Risebrough *et al.*	1968	Pigeons	PCBs	Increased steroid metab. in liver homogenates
287	Rehfield *et al.*	1971	Chickens	Aroclor 1248	Depression of secondary sexual characteristics
294	Platonow & Funnell	1971	White Leghorn cockerels	Aroclor 1254, 500 ppm "250 ppm/13 wk	Decreased development of comb and wattles Testicles decreased to 50%
295	Platonow & Funnell	1972	White Leghorn cockerels	PCBs, 500 ppm/4 wk	Lower comb and testicular weight
290	Nowicki and Norman	1972	1 wk old	Aroclor 1254 & 1260	Increase in the metab. of testosterone, estradiol-17β and 4-androstene-3,17 dione
296	Iturri	1974	Single comb white Leghorn cockerels	Various PCBs, Chronic 50–200 ppm oral adm.	Depression of secondary sexual characteristics Decreased testes weight
245	Lincer & Peakall	1970	American kestrels	Cockerels inj. with Aroclor 1254 & 1262	Dose-dependent microsomal breakdown of estradiol to a more polar metabolite in liver
170	Anonymous	1970	Ring doves (F)	PCBs 10 ppm/3 wk	Lowered estrogen levels
145	Oerberg & Lundberg	1974	Mice, castrated (M)	Clophen A60 0.25 mg/d. during 28 days	Decreased seminal vesicles in testosterone propionate treated animals
288	Bitman & Cecil	1970	Rats (immature)	PCBs 1221–1248 One inj. PCTs	Low estrogenic activity Low estrogenic activity
306	Second report for Yusho	1971	Rats (castrated) Rats (immature)	PCBs PCBs	Potentiation of uterotropic action of estradiol (it did not increase the uterine weight) Increased uterine weight and uterine glycogen
241	Bitman *et al.*	1972	Rats (immature)	PCBs	Low estrogenic activity
293	Nelson	1974	Rats (immature)	PCBs	Inhibition of 17β (^{3}H) estradiol binding to uterine receptor
207	Jonsson *et al.*	1976	Rats (F)	PCBs 75 ppm/8–36 wk 150 ppm/8–36 wk	Reduction of plasma progesterone Histologic changes in ovarian stroma
291	Platonow *et al.*	1972	Boar (adult)	Aroclor 1254 10 & 100 mg	Reduced urinary estrogen and dehydroepiandrosterone (with the higher dose)
297	Nagai *et al.*	1969	Man	Yusho patients	40% showed elevated urinary androsterone etiocolanolone and dehydroepiandrosterone
302	Wassermann & Wassermann	1972	Rats	PCBs 1221	Ultrastructural feature of adrenal zona fasciculata hyperfunction
303	Wassermann & Wassermann	1973	Rats	PCBs 1221	Increased plasma corticosterone levels
304	Flick *et al.*	1965	Rats	Aroclor 1242 200 ppm	Enlarged adrenals
305	Wassermann *et al.*	1976	Rats	Aroclor 1254	Ultrastructural features of hyperfunction of β-cells of the endocrine pancreas
299	Wassermann & Wassermann	1973	Rats	Aroclor 1221 Aroclor 1254	Decreased PBI serum levels. Ultrastructural features of hyperfunction of the thyroid cells
300	Rastomsky	1974	Rats	Aroclor 1254 i.p. 25 mg/kg/d/4 d	4–5 fold increase in biliary excretion of ^{125}I-thyroxine. Increased biliary ^{125}I-thyroxine glucuronide. Enhanced uptake of ^{131}I. Reduced serum PBI levels. Reduced binding of thyroid hormones to serum proteins
301	Hurst *et al.*	1974	Bobwhite quail	PCBs 500 ppm	Enlarged thyroid glands. They took up more iodide.

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In contrast, corticosterone was found to be increased in the plasma of rats treated with PCBs,[307] and the adrenal zona fasciculata in these rats showed ultrastructural features of hyperactivity.[307] Enlarged adrenal glands were reported in cockerels given Arochlor 1242 in the diet.[306] This effect on glucocorticoids may be a consequence of a need for higher levels of glucosteroids as a defense against the stressor character of PCBs and perhaps also of the need for the catatoxic activity of corticosteroids.

The increased level of glucosteroids may produce in its turn, other biologic effects as a chain reaction to persistent heterostasis. Such may be the case of the immunosuppressive effect of PCBs and the hyperactivity of the β-cells of the endocrine pancreas. Ultrastructural features of hyperactivity were reported in the β-cells of the endocrine pancreas of rats given PCBs.[305] These findings were considered to be a result of solicitation of β-cells for carbohydrate homeostasis.

Effects of PCBs on the Immunologic Defense System (Table 22)

Decreased weight of lymphoid tissues in chickens[275,291,304] and in rabbits,[275] marked decrease in spleen weight in penned pheasants,[174] in single-comb white Leghorn cockerels,[296] and in rats,[301] atrophy of the thymus cortex and reduction of lymph nodes in rabbits,[279] and decrease in the bursa of Fabricius and spleen weight in progeny of chickens[307] were reported after PCB administration.

Decrease in total proteins and IgG were obtained in rats during subacute exposure to Aroclor 1221. The effect was higher than with DDT.[308] Decreased antibody response in chickens,[307] decreased serum antitoxin titers to tetanus toxoid and delayed hypersensitivity to tuberculin in guinea pigs[282] and a lower number of antitoxin-producing cells in the popliteal lymph nodes in guinea pigs given tetanus toxoid[309] were obtained with commercial mixtures of PCB.

In Yusho patients, a decrease in IgA and IgM and an increase in IgG were reported 2 years after the accidental alimentary poisoning.[310] Lower IgM levels were found in Yusho patients showing chloracne.[311]

Increased susceptibility to fungal disease in esturarine fish,[312] an increased susceptibility to hepatitis virus in Mallard ducklings,[313] an increased incidence of pneumonia and lung and intracranial abscesses in rats,[314] and an increased incidence of pneumonia and diarrhea in monkeys[315] were obtained experimentally with PCBs.

Chronic airway infections that persisted for several years were found in the majority of Yusho patients.[316]

From the experimental work and from the accidental poisoning which happened in Japan, it appears that the decreased immunologic response produced by PCBs may result in increased susceptibility to viral, bacterial, or fungal diseases.

The increased level of glucosteroids in animals given PCBs[303] may partially explain the reduced activity of the immunologic system. The fact that DDT also has been shown in animal experiments to reduce the immunologic response, though to a lesser degree[308] and in the absence of an increased glucosteroid plasma level, suggests the existence of more than one mechanism for the decrease in the immunologic response by means of organochlorine compounds.

Effects of PCBs on the Nervous System (Table 23)

An uncoordinated locomotor activity was reported in the veil-tailed goldfish kept in water containing 5 ppm Clophen A50.[318] An increased locomotor activity was

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TABLE 22

EFFECTS OF PCBs ON THE IMMUNOLOGIC DEFENSE SYSTEM

Ref.	Authors	Year	Species	Compound, Dosage	Biologic Effects
312	Hansen *et al.*	1971	Estuarine fish	Aroclor 1254	Increased susceptibility to fungal disease.
301	Flick *et al.*	1965	Chickens	PCBs	Atrophy of lymphoid tissues
313	Friend & Trainer	1970	Mallard ducklings 10 d. old.	Aroclor 1254, 0, 0, 25, 50, 100 ppm	Increased susceptibility to duck hepatitis virus, 14, 35, 65, 94%; mortality respectively.
281	Vos & Koeman	1970	Chickens	PCBs	Atrophy of lymphoid tissues.
275	Vos	1972	Chickens	PCBs	Atrophy of lymphoid tissues.
174	Dahlgren *et al.*	1972	Penned pheasants	Aroclor 1254 1:9 in corn oil	Marked splenic atrophy in the dead birds. (300–400 ppm PCBs levels in brain tissue).
296	Iturri	1974	Single comb white Leghorn cockerels	Aroclor 1254 chronic oral adm.	Decreased spleen weight.
307	Harris	1976	Chickens	PCBs	Decreased antibody response and decrease in Bursa of Fabricius and spleen weight in progeny.
279	Vos & Beems	1971	Rabbits	PCBs	Atrophy of the thymus cortex. Reduction of lymph nodes.
275	Vos	1972	Rabbits	PCBs	Atrophy of lymphoid tissue.
308	Wassermann *et al.*	1973	Rabbits	Aroclor 1221 250 ppm/3 m.	Decrease in total proteins and IgG. (More than with *p,p'*-DDT).
281	Vos & Koeman	1970	Rats	Phenchlor DP6 2%o	Small spleens.
314	Kimura & Baba	1973	Rats	Kanechlor-400 in diet.	Increased incidence of pneumonia. Lung and intracranial abscesses.
316	Shigematsu *et al.*	1974	Rats	PCBs	Increased number of lysosomes and large vacuoles in alveolar macrophages.
282	Vos & Van Driel-Grootenhuis	1972	Guinea pigs	Aroclor 1260 Clophen A60 50 mg/kg	Decreased serum antitoxin titres, delayed hypersensitivity to tuberculin, atrophy of the thymus.
309	Vos & Roij	1972	Tetanus toxoid	Aroclor 1260 0, 10, and 500 ppm for 8 wk	Significant reduction of immunoglobulins. Lower number of antitoxin-producing cells in the popliteal lymph nodes.
315	Nishizumi	1970	Monkeys	PCBs	Pneumonia or diarrhea were the main causes of death
317	Allen & Norbach	1973	Rhesus monkeys	PCBs	Lymphopenia
310	Shigematsu *et al.*	1971	Man	Yusho patients	Decrease in IgA and IgM and increase in IgG, two years after the alimentary poisoning
311	Saito *et al.*	1972	Man	Yusho patients	Lower IgM levels in patients showing clearance
316	Shigematsu *et al.*	1974	Man	Yusho patients	Chronic airway infections that persisted several years

TABLE 23

EFFECTS OF PCBs ON THE NERVOUS SYSTEM

Ref.	Authors	Year	Species	Compound, Dosage	Effects
318	Hattula & Karlog	1972	Weil-tailed goldfish	Clophen A50 5 ppm in water	Uncoordinated movements.
319	Ulfstand *et al.*	1971	Robins	Clophen A50, 5 μg inj. into mealworms	Increased locomotor activity. PCB residues level in the breast muscle was 4 times that in controls
320	Karlsson *et al.*	1974	Red starts	PCBs 11 μg into mealworms/d/12 d	Increased locomotor activity during the early night hours, at the peak of normal migratory activity. The residue levels were as those reported for wild birds.
174	Dahlgren *et al.*	1972	Penned pheasants	Aroclor 1254 in corn oil, 12.5 & 50 mg/wk	The ability to avoid hand capture was less efficient in the offspring.
321	Kreitzer & Heinz	1974	Coturnix quail	Aroclor 1254 in diet 200 ppm/8 d at 7 d of age followed by 6 d of normal diet	Group avoidance response significantly suppressed No recovery was observed. Increased mortality from predators may occur.
322	Fukuda	1972	Rats	Kanechlor-400 100 mg/kg/d/12 d 300 mg/kg/d/6 d	Changes in cortical evoked responses elicited by stimulation of sciatic nerve: high N_2 waves and lack of N_3 waves.
324	Fukuda *et al.*	1974	Rats & mice	Kanechlor-400	No effect on the maximal electroshock seizure in mice.
225	Iatropoulos *et al.*	1977	Rhesus monkeys	Clophen A30 4, 16, 64 mg/kg/28 d	Central nervous system degenerative changes due to secondary hypoxia (reversible changes in the endothelium of small vessels).
323	Murai & Kuroiwa	1971	Man	Yusho patients	Numbness or pains in arms and legs. Decrease in the conduction velocity in peripheral sensory nerves (in the radial or sural nerves or both)

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obtained in robins fed Clophen A50-injected mealworms.[319] and in redstarts given 11 μg PCBs (in mealworms) per day, for 12 days.[320] The increased locomotor activity in redstarts began during the early night hours at the peak of normal migratory activity.

Offspring of penned pheasants given Aroclor 1254 in corn oil, 12.5 and 50 mg per week were less able to avoid hand capture.[233] The group-avoidance response was significantly suppressed in coturnix quail treated with 200 ppm Aroclor 1254 for 8 days, beginning at the age of seven days and followed by 6 days of normal diet.[320] Such effects in birds naturally exposed to PCBs may cause increased mortality from predators.

Changes in cortical-evoked responses elicited by stimulation of the sciatic nerve, high N_1 waves and lack of N_1' waves were noted in rats given Kanechlor-400.[322] Decrease in the conduction velocity in peripheral sensory nerves and numbness and pains in arms and legs were reported in Yusho patients.[323]

Degenerative changes in the myelin sheath of nerve fibers and in the brain were described in Rhesus monkeys given Clophen A30 for 28 days. The brain lesions were attributed to reversible changes, produced by PCBs, in the endothelium of small vessels, which lead to secondary hypoxia.[324]

Dermatologic Effects of PCBs (Table 24)

Hyperplasia and hyperkeratosis of the epidermal and follicular epithelium were obtained with Phenchlor DP6 and Clophen A60 in rabbits.[279] Aroclor 1260 in dermal application gave less severe skin lesions, as compared with the above mentioned compound.[222,279] whilst 2,4,5,2',4',5'-hexachlorobiphenyl produced moderate skin lesions.[222]

Other authors found that the skin lesions produced by technical compounds in rabbits were identical to those produced by pure chlorinated biphenyls (hyperkeratosis, dilatation of hair follicles and cysts filled with keratinous material).[325]

In Rhesus monkeys given 25 ppm Aroclor 1248 in the diet, loss of hair and acne occurred after one month.[326] *Macaca mulatta* monkeys given 100 or 300 ppm Aroclor 1248 in the diet had lost, within 3 weeks to 1 month, most of their hair and eyelashes. The eyelids and the mouth were edematous. Small comedones appeared on the cheeks and the neck. Erythema and acne of the face and neck developed within 1–2 months. The lesions were severe in females and moderate in males. The major microscopic changes were of large intrafollicular keratin cysts and epithelial hyperplasia of the hair follicles, particularly of the face.[187]

In occupationally exposed persons, skin lesions were noted.[127] Cases of chloracne were reported among workers exposed to these compounds for 19 months.[327] Three cases of malignant melanomas, in persons occupationally exposed to PCBs, were ascribed to the carcinogenic effects of PCBs,[328] although, other compounds to which those patients were exposed concomitantly could be charged with the responsibility.[329]

In Yusho patients, pigmentation of the skin, nails, and gingiva, and chloracne eruptions appeared.[330,331] Hypersecretion of Meibomian glands was also reported.[330] The severely affected patients showed no spontaneous improvement in their cutaneous manifestations.[332] In Yusho babies, chloracne and a dark discoloration of the skin and mucous membranes, resembling that of Addison's disease was found to occur.[206,314]

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TABLE 24

DERMATOLOGIC EFFECTS OF PCBs

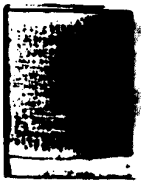
Ref.	Authors	Year	Species	Compound, Dosage	Effects
318	Hattula & Karlog	1972	Weil-tailed goldfish	Clophen A50 5 ppm in water	Change in skin color (orange to pale yellow)
279	Vos & Beems	1971	Rabbits	Phenchlor DP6	Reddening of skin, transverse wrinkling, hyperplasia, and hyperkeratosis of the epidermal and follicular epithelium
				Clophen A60	Less marked effects and minimal hyperplasia and hyperkeratosis of the follicular epithelium
				Aroclor 1260 (dermal application)	Severe skin lesions
222	Vos & Notenboom	1972	Rabbits	Aroclor 1260 2,4,5,2',4',5'-hexachlorobiphenyl	Less severe skin lesions.
325	Komatsu & Kikuki	1972	Rabbits	Kanechlor-400	The skin lesions produced by technical compounds were identical to those produced by pure chlorinated biphenyls (hyperkeratosis, dilatation of hair follicles and cysts filled with keratinous material).
				Kanechlor-500 3,4,3',4'-tetrachlorobiphenyl	
326	Allen *et al.*	1974	Rhesus monkey	Aroclor 1248 25 ppm/2 months	Loss of hair and acne occurred after one month
187	Allen	1975	Macaca mulatta monkeys	Aroclor 1248 100 or 300 ppm/2–3 m	Within 3 wk–4 m, the animals had lost most of their hair (face, head and neck), the mouth and eyelids were edematous and small comedones appeared on the cheeks, the neck and around the mouth. The major microscopic changes were of large intrafollicular keratin cysts, epithelial hyperplasia of the hair follicles, particularly of the face.
				Aroclor 1248 2.5 or 5.0 ppm	Facial edema, alopecia, erythema and acne that involved the face and neck developed in 1–2 months. The lesions were severe in females and moderate in males.
178	Hasegawa *et al.*	1972	Man	Occupational exposure	Skin lesions were noted.
323	Meigbs *et al.*	1954	Man	Occupational exposure	Cases of chloracne among the workers exposed for 19 months.
330	Toshitani	1972	Man	Yusho patients	Acneform eruptions in covered areas. Improvement in exposed areas.
331	Urabe	1974	Man	Yusho patients	Muco-cutaneous symptoms. Hyperpigmentation of gingiva. Hypersecretion of Meibomian glands.
332	Khusa *et al.*	1974	Man	Yusho patients	The severely affected patients showed no spontaneous improvement of cutaneous manifestations.
204	Miller	1974	Man	Yusho babies	Chloracne in 10 cases.
214	Fitzmorris	1974	Man	Yusho babies	Peculiar dark color of skin and mucous membranes resembling those found in Adisson disease.

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TABLE 23

TUMORIGENIC EFFECTS OF PCBs

Ref.	Authors	Year	Species	Compound, Dosage	Effects
9	Falkmer *et al.*	1977	Hagfish of fjord of open sea	Naturally occurring	Hepatomas 5.8% in 1972 and 0.6% in 1973–1976 Hepatomas 2.8% in 1972 and 0.9% in 1973–1976 Islet cell neoplasms and hamartomas 0.5%, and less than 0.1% for the surveys of 1972 and 1973–1976 for the fjord and open sea hagfish
328	Bahn *et al.*	1976	Man	Occupational exposure	Melanoma
221	Ito *et al.*	1973	Mice	*Kanechlor*-500 in diet 500 ppm/12 m	Nodular hyperplasias and well differentiated hepatocellular carcinomas in the liver Promotion of carcinogenesis by α-BHC and β-BHC
333	Kimbrough *et al.*	1974	Mice	Aroclor 1254	Hepatomas and adenofibrosis
334	Nagasaki *et al.*	1974	Mice	Kanechlor-500 500 ppm/ α-BHC 250 ppm/24 wk	32 wk Neoplastic changes in liver
				Kanechlor-500 100 ppm + α-BHC 50 ppm	32 wk Neoplastic changes in liver
337	Nagasaki *et al.*	1975	Mice	Penta- tetra- or trichloro-biphenyls, 100, 250, 500 ppm for 24 wk	Liver tumorigenesis in higher incidence at higher dose rates.
				Penta- and tetra-chloro-biphenyl 100 ppm + 50 ppm α-BHC	Liver tumorigenesis of α-BHC was promoted also by pure chlorinated biphenyls.
314	Kimura & Baba	1973	Rats	Kanechlor-400 (1000 1500 mg—the total for 400 days)	Tumoral liver change in 6/10 females and 0/10 males.
336	Makiura *et al.*	1974	Rats	Kanechlor-500	Inhibited the induction of liver tumors by several liver carcinogens.
337	Kimbrough *et al.*	1975	Rats (F)	Aroclor 1260 100 ppm/21 m	Hepatocellular carcinomas 26/184 Hyperplastic nodules 146/184 Adenofibrosis
338	Wassermann *et al*	1978	Rats (F)	Aroclor 1254 200 ppm/25 m	Hepatocellular adenomas.
339	Kimura *et al*	1976	Rats	PCBs	Promotors in experimental carcinogenesis
340	Allen & Norbach	1973	Rhesus monkeys	Aroclor 1248 300 mg/kg PCTs 5000 mg/kg	Hyperplasia and dysplasia of gastric mucosa with invasion of adjacent tissues.



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Tumorigenic Effects of PCBs (Table 25)

Carcinogenicity in animal experimentation is one of the tests for toxicity of environmental chemical pollutants. Experimental studies of the carcinogenicity of PCBs were carried out in rodents. Hepatocellular adenomas, carcinomas, and adenofibrosis were obtained in mice with commercial mixtures of PCBs[222,331,334] and with pure biphenyl compounds[335] and in rats with technical mixtures of PCBs.[316,336-338] The incidence of the tumors increased with the dosage.[335] Very high doses were needed to produce adenomas in male rats.[336] *The administration of technical PCBs or of pure* chlorinated biphenyls (tetra- and penta-chlorobiphenyls) together with α-BHC, in doses which given separately would have no carcinogenic effect, induced liver tumors.[335,339] These facts suggest that PCBs may act as promotors of experimental liver carcinogenicity. For other hepatocarcinogens like 3'- methyl - *p* - dimethylazobenzene, *N*- 2 - fluosenyl acetamide and diethylnitrosamine. PCBs proved to be inhibitors of carcinogenesis.[336] Hyperplasia of the epithelium of the hair follicles, particularly of the face and severe hypertrophic and hyperplastic gastritis, were *produced experimentally in adult monkeys.*[339]

Hepatomas and islet-cell hamartomas and neoplasms occurred in cyclostomes, particularly in hagfish in the Gullmar fjord, Sweden, and in deep sea waters. The incidence of these tumors was 5.8% for hepatomas in the Gullmar fjord hagfish and only 2.8% for those collected at open sea, some 12 km from the coast, in 1972. In 1974–1976 these percentages became 0.6 and 0.9% respectively. Islet cell hamartomas and frank neoplasms, which were found in 0.5% of cases in 1972, decreased to less than 0.1% in 1974–1976. Subcutaneous and mesenterial neoplasms were occasionally observed. PCB levels of 5.0 ppm and 0.1–0.4 total DDT were found in fjord hagfish livers and only 0.2 ppm PCBs in open sea hagfish.[6]

Two malignant melanomas were found in a group of 31 persons occupationally exposed to PCBs. An incidence rate of only 0.04 malignant melanomas would be expected for this group. Another case, out of a group of 41 persons occupationally exposed to PCBs, was also reported.[320] There is no general agreement concerning the induction of melanomas by PCBs, since it seems that the group of workers mentioned was exposed concomitantly to other carcinogens, especially epoxides.[329]

Summary

PCB residues are found in biota all over the world. A biologic magnification of PCBs has been demonstrated in the food chain: plankton-fish-fish eating birds.

A world map of the PCBs residues in biota and some of their biologic effects are given in this study.

The biologic effects of PCBs are varied and may generally be explained by the induction or inhibition of the activity of a large number of enzymes, which upsets quantitatively, normal biochemical processes. Harm to reproduction, growth, development, defense systems, tissues, and organs appeared in susceptible organisms as a result of such changes or as a chain reaction to heterostases. The adverse health effects, observed in persons occupationally exposed and in those accidentally poisoned, point to the risk for the general population of an ever-increasing environmental pollution by PCBs.

There is need for an integrated approach, consisting of epidemiologic studies on high risk groups in the general population and in persons occupationally exposed, as well as periodic assessment of PCB residues in man, his food, and feed supplies.

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